PB84-227008

Selected Approaches to Risk Assessment for Multiple Chemical Exposures: Appendix

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jun 84

U.S. Department of Commerce
National Technical Information Service
NTIS

PB84-227008

EPA-600/9-84-014b
June 1984

SELECTED APPROACHES TO RISK ASSESSMENT FOR MULTIPLE CHEMICAL EXPOSURES: Appendix

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NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA-600/9-84-014b

2.

3. RECIPIENT'S ACCESSION NO. PB84 227008

4. TITLE AND SUBTITLE
Selected Approaches to Risk Assessment for Multiple Chemical Exposures: Appendix

5. REPORT DATE June 1984

6. PERFORMING ORGANIZATION CODE

7. AUTHOR(S)
Dr. Jerry F. Stara and Dr. Linda Erdreich

8. PERFORMING ORGANIZATION REPORT NO.

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Same as Item (12)

10. PROGRAM ELEMENT NO.

11. CONTRACT/GRANT NO.

12. SPONSORING AGENCY NAME AND ADDRESS
Environmental Criteria Assessment Office
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

13. TYPE OF REPORT AND PERIOD COVERED

14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This appendix to "Selected Approaches to Risk Assessment for Multiple Chemical Mixtures: Progress Report on Guideline Development at ECAO-Cin" contains post-meeting comments on the issues sent by the peer reviewers of the workshop, plus selected references pertaining to the guidelines. All pertinent comments have been addressed in the primary report.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT
Public

19. SECURITY CLASS *(This Report)* Unclassified

20. SECURITY CLASS *(This page)* Unclassified

21. NO. OF PAGES 162

22. PRICE

NOTICE

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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SECTION 1

INTRODUCTION

This is the appendix to the report entitled "Selected Approaches to Risk Assessment for Multiple Chemical Exposures." It contains the postmeeting responses, in the form of memoranda, of workshop participants. The participants were asked to comment on each consensus topic, pointing out the extent of consensus and obstacles to agreement, and to elaborate on topics of particular interest that were presented or discussed in the workshop sessions. Also included in this appendix are a list of references cited in the postmeeting memoranda and copies of two background references (Stara et al., 1981; Crump and Howe, 1983) that were distributed to the participants prior to the meeting.

SECTION 2

POSTMEETING MEMORANDA

Julian B. Andelman
August 4, 1983

Postmeeting Memorandum

Workshop of Risk Assessment for Multiple Chemical Exposure, EPA, Cincinnati, Ohio, July 12-13, 1983

PART I. CONSENSUS TOPICS

A. Interspecies Conversion of Dose and Duration of Exposure

A considerable portion of the discussion was devoted to the question of the power of the animal weight that should be used in comparing doses between species (e.g., the one-third power) and similarly the power of time (e.g., square root of time). Clarkson noted that the ratio t1/2/m1/3 seems to be constant among species for methyl mercury. There seemed to be a consensus that such an approach was useful, but disagreement as to what the exact mathematical relationship might be. There was no systematic presentation of the options and sufficient experimental data to back them up. It is likely that there are differences among chemicals and not a constant relationship to use among all species. Thus, it may be important to in fact develop more than one relationship. Therefore, I recommend that an analysis of actual data and models be developed, and that, based on it, a judgment made as to the possible range of relationships to be used. It was not clear to me, based on the discussion, that an obvious single relationship is applicable.

B. Health Risk Assessment for Less than Lifetime Exposure

Crump's mathematical treatment is elegant and well-presented. One question is whether it can be used in fact to distinguish between stage of carcinogenesis and thereby be applied to assess whether an earlier or later period of exposure was more important. Enterline noted that his work on arsenic-induced lung cancer was not able to effectively distinguish among stages by such a model. Another issue relative to the Crump model is whether the concentration term (dose) can be effectively dealt with when it is not a first-order variable (e.g., concentration to to the 1.2 power). This seems to be a not uncommon situation and should be an essential part of the model. For example, in the EPA Water Quality Criteria Document for Arsenic, the fit of the epidemiological data to a model indicates such a non-linear dose factor.

C. ADI's Based on Quantal, Continuous or Graded Data

The goal of this discussion should be to develop an approach which would determine an ADI which would be protective of a defined percentage of the population with a given probability or uncertainty. Thus, it should not be to establish such a level protective at a 100 percent certainty. Then, once such an ADI is determined, a safety factor (not an uncertainty factor) can be incorporated. Presumably the uncertainty factor will already have been incorporated into the ADI, initially.

On this basis, it should be decided as to which specific effects are to be incorporated into the ADI. That is, should it include simply esthetic effects, such as organoleptic ones or only frank disease effects. The EPA Interim Drinking Water Regulation distinguish Primary (health related) and Secondary (aesthetic and other) effects which are regulated differently. The approach by Yves Alarie in his article "Dose-Response Analysis in Animal Studies: Prediction of Human Responses" should be considered. (Alarie, Env. Health Perspectives, 42, 9-13, 1981). For sensory irritants he showed how the effects of respiratory rates in animals could be used to predict varying intensities of responses in humans.

D and E. Route-to-route Conversion and Mutiple Chemical Assessment

These topics are related and will be considered together. Durkin presented the approach of summing the exposure/ADI for each chemical when a multiple chemical exposure is involved. As discussed, one important factor is whether chemicals act in concert to cause the same type of effect. That is, if they are independent in their actions involving different target organs, such additivities of exposure/ADI are irrelevant in terms of predicting when there may be a critical level exceeded. A second factor to consider is whether the fact that the sum of such ratios happens to exceed unity should be a critical point in deciding whether the population has been exposed to a critical quantity of chemicals. This could be very misleading, again, if there is no understanding of whether the effects are independent. It seems to me that before such a "single number" approach is developed, some further consideration should be given to it and, specifically, a presentation developed which considers actual experimental data.

With respect to route-to-route conversion, we seem to be discussing only broad principles here and have not yet considered a sufficient number of examples to take us beyond the Stokinger-Woodward model. It seems that there are two possible approaches to use in the absence of detailed experimental data: first, to assume complete absorption by both routes (oral and inhalation) and then simply predicting an effect in one from the other. This would, however, not necessarily be conservative, since there would be a chance, depending on the relative amount of absorption by the two routes, for underestimating the dose for the second route from the first. A second approach would be to establish a range of relative exposures from an analysis of various chamicals and their different routes, the example being the work of Pozzani et al, in Amer. Industrial Hygiene Journal, 20:364-369 (1959).

PART II. NEW TOPICS

A. Structure Activity Relationships

Enslein discussed the use of structure activity, (S-A) relationships, particularly to see if concordance could be shown between a qualitative prediction of an effect and the S-A approach. The success for qualitative predictability is impressive, but the real need here is for obtaining quantitative relationships. Although the use of S-A was shown to be very advanced in aquatic toxicity, it may be too early to use it for our purposes.

B. Reproductive Effects - No comments

C. Use and Biological Justification of Math.Models -

One important area seems to have to not been covered in this discussion, namely the need to deal with a population distribution in assessing exposure and risks, as well as the distribution of chemicals in such a population. Thus, even if there is a nominal constant concentration in water or air, the behavior of the people will result in a distribution of actual exposures which can be quite varied and should be factored in to the analysis.

PART III. WORKGROUPS

A.1 Sensitive subgroups

There is one issue not discussed which I would like to mention. There may be sub-groups which are particularly sensitive to one agent as a result of their exposure to another. For example, there is clear evidence that incidence of non-melanoma skin cancer is related to exposure to UV-B sunlight. There is also some evidence that arsenic exposure might promote this effect. Such relationships could be considered in the framework of sensitive subgroups.

A.2 Ranking the Severity of Effects

It seems that a ranking scheme should only be developed and should not be a "seat-of-the-pants" approach. That is, whether liver damage is a more harmful effect than kidney damage should only be decided after these principles are set forth.

B.1. Multiple Route Exposures

The question of multiple route exposure evaluation is more directly considered under that of route-to-route extrapolation, at least in terms of equivalency of effect. In terms of assessing actual exposures this is not different than that of evaluating exposure via any given route. However, I would like to draw attention to the growing evidence that off-gassing of volatile chemicals from water used in the home can creat an air exposure separately from that of the direct ingestion of the water.

B.2. Use of Exposure Data in Assessing Health Risk

As part of the "writing" team for that group, I have nothing further to add.

Postmeeting Memorandum of Eula Bingham

CONSENSUS TOPICS

I. Interspecies conversion of dose and duration of exposure

A. EPA approach

The approach by EPA in setting Water Quality Criteria has been to use the factor mg/m^3 in making interspecies conversions of dose and the fraction of life span for the duration of exposure (non-cancer effects).

B. Consensus

It was the consensus that using the mg chemical/cm^2 body surface area per day was probably the best that could be done and does offer advantages over mg chemical/kg body weight per day. The only viable option currently for duration is using fraction of life span.

C. Obstacles

The major obstacles are that none of these factors alone will provide perfect equitoxic doses since the differences among species cannot be accounted for by these simple terms, however to be more precise requires more data on functional differences not just more complicated mathematical modeling of an inadequate data base.

II. Health risk assessment for less than lifetime exposures

A. EPA approach is to use actual studies for determining criteria for aquatic organisms and the only human health calculation involves dividing the subchronic exposure level by 10 to estimate a corresponding chronic level. (reverse procedure chronic ⟶ subchronic has not been done)

B. Consensus

It appeared to me that the group was in favor of using all the data to calculate the best fitting NOAEL.

C. Obstacles

A major obstacle is the lack of data at various exposure durations so it was considered the best recourse to use all data in making any estimate.

III. Carcinogen

A. EPA approach

Currently the agency bases lifetime cancer risks from durations less than a lifetime on the ratio of exposure total dose to the total dose associated with a given cancer potency and lifetime cancer level.

B. Consensus

The consensus was to use the multistage model (Crump and Howe, 1983) described at the meeting by Dr. Crump.

C. Obstacles

Probably fewer than for most of the other consensus issues but still data are missing to validate.

IV. ADI's based on quantal, continuous or graded data

A. EPA approach

The current approach by EPA is to use a safety factor approach. The goal of this group was to select a method for estimating ADI's using quantal or continuous data.

B. Consensus

It was not clear to me that there was a consensus.

C. Obstacles and other

The obstacles are clearly the disadvantages raised by Dr. Crump, mainly the nature of the toxic event should guide the choice of the model. For effects other than genetic in origin a linear dose response model may over estimate the true risk. From a public health view this is not such a handicap but from the view of establishing a cost-benefit analysis it may compromise the agency's position. It is probably worthwhile to use Crump's model to test a few chemicals (non-carcinogens) about which we have data to determine the usefulness.

V. Route to route conversion

A. EPA approach

Currently it has been the practice of the Agency to use inhalation data or TLV's to estimate oral route exposures using the Stokinger-Woodward method.

B. Consensus

It seemed to me that generally the group agreed with the proposition that Dr. Withey put forth that route to route conversions be limited to inhalation and oral routes as well as with the conditions he laid out as acceptable for extrapolation, i.e. 1.) portal entry is not target organ, 2.) toxicant is not totally inactivated prior to reaching target, and 3.) elimination rates are sufficiently slow that blood levels do not fluctuate greatly during dosing.

While I am in general agreement, it may be that Item 1 is always necessarily required.

VI. Multiple Chemical Assessments

A. EPA approach

It was not clear what the current approach is except that for carcinogens the approach is to multiply or add up the risks (with such small numbers there is essentially no difference).

B. Consensus

There was really only time to hear Dr. Durkin present the issue and options.

C. Obstacles

Lack of time to discuss this issue was inhibiting. If I had to select one option I would probably go with #2, but I am not satisfied with many of the assumptions, e.g. two tumors in the same organism are no worse than one tumor. The judgment runs contrary to the way experimental data on the potency of carcinogens has been judged by many investigators (Berenblum, Shubik _et al_.).

VII. Workshop - Considering high risk subgroups in health risk assessment

A. The question of how to account for sensitive subgroups in a population is one that the group has discussed previously. During this session this participant acted as the moderator. A series of questions were posed to the group.

B. Consensus (Dr. Schneiderman took notes and will provide those.)

Generally the group agreed that it would be worthwhile to explore the development of criteria defining specific high risk groups. It seemed reasonable to come up both with lists of chemicals to which there are hyper-sensitivities and to identify groups of people who may be at special risk. A number of suggestions for how to go about this were given (see individual reports).

These include disease registries, estimates of populations with various disease states, e.g. asmatics, heart disease, renal failure, etc. Another suggestion was how much more susceptible are children than adults to carcinogens using animal and (human) data bases.

Biochemical, enzyme, and/or pharmacokinetic variations can be used to reach certain conclusions regarding variability.

My impression was that there was consensus regarding the usefulness and importance of bringing this information together.

C. Obstacles

Major obstacles were finding the data in the literature or within various agencies. It seems to me that one or two of the participants can help with this problem.

VIII. Workshop on Ranking the Severity of Effects

A. Apparently the main issue in this workshop was whether or not a "proposal" in the Federal Register had used an appropriate grading system.

B. Consensus

My impression was that there was massive confusion and no real conclusions came out except there were many questions about the ranking scheme. The use of terms made me suspect that the weighting would cause a skewing of the scale.

Actually the terms used are somewhat vague and need to be more definitive in toxicological terms.

I felt that we had just begun the discussion and felt very uneasy about the session.

Edward Calabrese July 19, 1983

Postmeeting Memoranda

Consensus Topic: Alternatives to the NOEL Derivation Methodology

A. EPA proposes to derive an acceptable exposure level with the use of regression equations instead of simply dividing NOEL by 100 to achieve an ADI.

C. Comments:

It is a possible alternative requiring further evaluation. Future research needs to be directed toward identifying the distribution of sensitivities in the human population and how this knowledge could be used in the derivation process. Little work to date has been published on improving the biological plausibility of tolerance distribution models (e.g., logit-probit). Yet these are the very models which in principle are best suited for this approach. Until EPA is able to offer a reasonable prediction as to how the variability responses of the test group of animals corresponds to human variability, this approach will not be based on acceptable biological grounds. Thus, in principle, this is a good idea because it tries to stay close to the data. But unless we can relate the animal model more precisely to the human experience it offers little improvement over current approaches.

Workshop Topic: High Risk Groups

A. What role should high risk play in the EPA methodology for deriving acceptable exposure limits?

C. The general need in this area is that of research to identify and quantify potential high risk groups. Once that is accomplished, it is crucial to develop better dose-response data which are essential in the standard derivation process. As in many other cases discussed at the workshop, the policy issues are evolving much more rapidly than the science.

Workship Topic: Ranking Scheme for Dumpsites

A. EPA wants to develop an objective scheme for ranking wastesites.

C. The state of the art is so rudimentary that it is unwise to consider anything said at the workshop as more than a focus for discussion. The presentation should stimulate further thinking on the area, and a reassessment of underlying assumptions used.

July 27, 1983

TO: EPA and Dynamics Corp.

SUBJECT: Post-Meeting Memo

FROM: Tom Clarkson

Multiple Route of Exposure

Issue Can we sum exposures from different routes?

Properties/characteristics of compound to allow multiple route exposures (R. Hartung)

1) The dose-duration patterns should be identical for each route

2) Each route should produce identical systemic effects

3) There should be no effects at the portal of entry

4) There should be no first pass effects

5) The dose-response-time relationships should be known for at least one route of entry in terms of the actual absorbed dose

Data Base for Route to Route Extrapolation

Listed below in order of completeness are data bases ranging from ideal to virtually nil:

1) Dose-response-time relationship for all routes of exposure

2) Dose-response-time relationship for less than all routes but with pharmacokinetic data

3) Chronic data for one route but acute data for other routes and pharmacokinetic data

4) Acute data and pharmacokinetic data

5) Acute data only

6) Physiochemical data and structure - activity calculations (e.g. The Enslein approach)

With decreasing data bases it is assumed that increasing large safety factors will be needed in relating route to route extrapolations.

A number of complications were discussed for route to route exposure. First pass effects and route specific effects, e.g. dioxin, gives both lung and liver tumors by inhalation but only liver tumors by oral intake.

Dr. Pepelko took extensive notes of the group meeting on Route to Route exposure and will put together the consensus report. It was agreeed that members of the group would send their notes to him.

CONSENSUS OPTIONS

1. Intraspecies conversion of dose and duration of exposure for non-cancer effects

It was agreed that corrections for less than life-time exposure would be made for subchronic and chronic exposure only. The corrections would be based on the equivalence of fractions of life-span. The corrections would not be made for acute exposures. Equitoxic dose routes would continue to be calculated using the cube-root body weight conversion. However, it was agreed that this subject required further attention. More attention should be given to quantitative physiological parameters available in the extensive literature on comparative physiology. A general approach would involve two steps:

STEP 1: Correction for differences in volume of distribution. In general, this would be on a body weight basis unless there was information on distribution to specific physical and chemical compartments of the body. For example, if the agent distributed to the skin, a surface area conversion would be appropriate.

STEP 2: This should take into account systematic species differences in rates of elimination of compounds (excretion-metabolism-inactivation). Probably small species such as rodents eliminate chemicals more rapidly than larger species. The question arises as to how to eliminate this systematic difference. It was noted that many functions related to rates of elimination are approximately at 2/3 power function of body weight viz. basal metabolic rate, rate of urinary excretion.

It was agreed that STEP 2 permits further research and evaluation.

II. Health Risk Assessment for Less Than Life-Time Exposures

It was agreed that the procedure described by EPA staff was the best available. For carcinogens the procedure described by Crump (Option 2) was the best available.

III. ADIs based on quoted dose response data

It was agreed that future estimates of ADIs should involve all the dose-response data and involve a calculation of a "quasi" ADI. This might be set at a 10^{-1} and 10^{-2} risk value (Option 2).

IV. Route to Route Conversion

This has already been discussed.

V. Multiple Chemical AH Assessment

Option 2 seemed to be more acceptable than Option 1. However, there are reservations about how the hazard should be calculated. The total hazard index formula proposed in Option 2 might be appropriate for similar chemicals, have common mechanisms of toxicity. However, it may not be useful to calculate a single number representing the total hazard from a mixture of very different chemicals. In this case, it would be better to look at each individual to see how it should be weighed in the evaluation of the overall hazard.

RISK ASSESSMENT FOR MULTIPLE CHEMICAL EXPOSURES
CINCINNATI, OHIO, July 12 - 13, 1983
H. CORNISH

I-V CONSENSUS TOPICS

A. The approach of EPA was to review the data available and previously discussed and then to see if a consensus could be reached on techniques for evaluation of human risk.

B. Consensus was apparently achieved on many of the approaches but always with the caveat that more research is needed and that we do not have enough information to do better.

C. The major obstacles to consensus are the degree to which individuals are willing to make "best extrapolations" from the data at hand. Some individuals will never be comfortable with any extrapolation while others are willing to acccept responsibility for making some kind of risk estimate on "available data."

D. Comments:

The first morning of the meeting contained a great deal of information from the previous meeting and did not incorporate much new material. Although the overview was necessary it should have integrated more of the new material for discussion. Dr. Durkin did present a new approach to multiple chemical assessment.

Interspecies conversions are often done on the basis of body weight or surface area. It was suggested that blood levels be emphasized and utilized wherever possible since this would represent a better measure of tissue exposure.

Route-to-route conversion evoked considerable discussion. It was pointed out that the Stokinger-Woodward model which has been used be EPA in some instances to convert from inhalation data to oral route suffers from a number of assumptions. This method, however, was initially utilized to provide the best possible estimate of a safe level of exposure for chemicals to which people were being exposed. Comparable today to dump site exposures. To say, for example that there is insufficient data to make an assessment of hazard at a dump site may be an abrogation of responsibility and turns the decision making process back to those who may be the least qualified. I believe I heard several suggestions that the "insufficient data" route be taken. This may be fine for potential exposure situations but is of no value whee an immediate exposure situation exists. Perhaps there needs to be some sort of separation of the "immediate crisis exposure extrapolation" from the "potential hazard exposure extrapolation." In the latter case it might be legitimate to hold making a decision until some additional identifiable data were available.

VI-VII WORKSHOP TOPICS

A. Workshop topics were reasonable well stated.

B. I'm not certain that a consensus was reached on these topics but they evoked considerable discussion and some suggestions for new approaches.

C. Major obstacles to consensus was lack of information on which one could make a decision.

D. Comments:

The discussions on structure activity relationships pointed out how they could be used in risk assessment but there was no presentation of examples of where it did work and where it didn't work.

Considerable discussion centered on multiple routes of exposure. Little information is available on which to base predictions of the contribution of the inhalation route plus the skin route or plus the oral route as simultaneous exposure routes. Mathematical models may be useful but research is certainly necessary in this area.

In the "use of experimental data in assessment of health risks" discussion it was pointed out that the data on hand at a dump site might include exposure concentration, duration of exposure, population at risk, along with identification of the major contaminants. To utilize this information to estimate health risks requires information on uptake, species biotransformation, and animal response to the individual chemical some would say. Hypersusceptible groups may require greater than normal safety factors. Although a risk estimate can be done using safety factors, measurement of safety factors in the exposed population might enhance the reliability of extrapolation. This may be true but I am afraid that for the most part the total available data base in animals lacks blood level data by which one could compare expected responses. This points out the need to encourage the determination of blood levels in animal toxicity testing.

It seems to me that discussion does not always lead to conclusions that are usable in risk assessment. Perhaps a future meeting could be an even more practical workshop. Several approaches could be used. Give two or three groups the identical chemical and the same toxicological information and see if they come up with comparable approximations of a safe exposure level. Another approach would be to give different groups the same chemical but with varying amounts of information. For example, can a group that has blood levels in the exposed population, knowledge of a hypersusceptible group, acute and chronic animal data really make use of that information and come up with a different estimate of a safe exposure level than the group with only some acute data. Perhaps they would come up with similar risk estimates but with different degrees of confidence in their assessment. The latter could often be the case since I'm not sure we really know how to make use of much of the data that may say we must have to make reasonable extrapolations to safe exposure levels. Actually a safety factor has often been factored in which expresses the degree of confidence in the data base.

POSTMEETING MEMORANDUM

To: Dr. Cipriano Cueto

From: Kenny S. Crump K. S. C.

Date: June 14, 1983

Subject: June 12-13, 1983 Workshop on Methodology for Risk Assessment for Multichemical Exposures

Once the general decision is made to adopt the multistage approach to estimating carcinogenic risks from less than lifetime exposure, there are a number of sub-issues to be decided--the number of stages and which stages to be allowed to be affected by the dose. In some cases when time-to-tumor data are available these can be estimated from the animal data. Otherwise, some value between 4 and 7, which is typical of human carcinomas, can be used for the number of stages. This may be the desired approach even when animal data are available. I concur with Arnold Kuzmack's suggestion that a table or tables appropriate for use with typical population distributions would be helpful. It may be that if the risk is averaged over ages of a typical population, the estimates will not depend greatly upon the number of stages or the number of dose-related stages, and, in fact, may give a result which is not very different from simply averaging the dose over the entire lifespan.

The calculation of a "benchmark dose" (or pseudo-NOEL, or whatever) appeared to meet with general acceptance, at least for quantal data. The risk for which the benchmark is computed needs to be selected. For moderately large quantal data sets, a risk of about 1% coupled with a 95% confidence limit appears to make the benchmark dose correspond roughly to the NOEL.

I wish that I had taken time in my presentation to describe and illustrate the benchmark approach to continuous data. The principal difference is that, instead of being defined in terms of a given increase in the response probability over that in the background group, the benchmark is defined as a lower statistical confidence limit for the dose for which the increase in the mean response over background is a given percent (say 1%) of the mean response in the unexposed population. It was pointed out that safety factors applied to benchmarks derived from quantal data may not be appropriate for those derived from continuous data. Also, other rationale for safety factors may need to be put forth for this case. The model used to calculate a benchmark dose does not appear to be critical so long as the risk value is between 1% and 10%. I personally prefer the polynomial regression models.

I liked the suggestion by Rolf Hartung that animal-to-human extrapolation factors might be determined empirically for non-carcinogens. Such a research project could shed some useful insights into the cross-species extrapolation problem. However, I think there is too much variability in the data for this to be done for single effects for single chemicals. It could be done for all data on a single effect, perhaps broken down into classes of chemicals.

The first step would be to collect the data. Perhaps the data base being assembled by ECAO could be used. Next a well-defined measure of potency would be estimated for each data set. This measure should relate to the response in the experimental range and have minimal statistical variability. The LD_{50} or the LD_{20} are potential candidates for acute effects. Next, an exploratory analysis would be conducted that relates the potency estimates for different species to a power of the body weight or some other physiologic parameter. This analysis could be used to determine if a correlation exists and, if so, what is the best method for cross-species extrapolation. The "best method" so determined would have a defensible scientific rationale, since it would be determined empirically from actual data. It probably would not coincide with mg/kg/day, mg/m^2/day, or any of the other methods considered by ECAO. Given sufficient data, the method could be made health-effect specific and also specific to different classes of chemicals.

KSC:skm
cc: Dr. Jerry Stara

MEMORANDUM

TO: Ciprian Cueto, Dynamac Corporation

FROM: Patrick Durkin, Syracuse Research Corporation P.D.

RE: Postmeeting Memo, July 12-13, 1983 Methodology Meeting for ECAO/Cin.

DATE: July 18, 1983

I. Interspecies Conversion of Dose and Duration of Exposure

A. ECAO has used the mg/unit surface area approximation of carcinogens and up until recently used only the uncertainty factor approach for non-carcinogens.

B. I perceived a consensus to accept the surface area approach for all compounds as a default position. Rolf Hartung's suggestion to let the available data set the exponent seemed to be generally accepted but examples are needed.

C. No major obstacles.

D. The papers referred to by Hattis and Clarkson deserve careful review. I will be doing this as part of another task for ECAO/Cin.

II. Less Than Lifetime Exposure for Carcinogens and Toxicants

A. ECAO has used the Druckery approach for carcinogens and has not formalized the approach for non-carcinogens.

B. The carcinogens led to a clear consensus to accept the Crump proposal except where clearly contradicted by available data. In such instances, ad hoc models based on the data should be used. For non-carcinogens, the approach recommended by ECAO had general acceptance but needs to be more formally articulated. I personally favor the blocking over the regression approach but either seems workable.

C. No major obstacles.

D. None.

III. ADI's Based on Quantal, Continuous, or Graded Data

A. EPA has not yet formally articulated a policy.

B. A universal consensus was not reached. I feel that it could have been reached if more time had been spent. I regard this more as a new topic than a consensus issue.

C. I don't think that any major technical issues need to be resolved to arrive at a reasonable default position. The major problem was that several of the participants did not have time to grasp the points which Dourson and Crump made.

D. Since this issue is somewhat complex, the lack of consensus is understandable. I think that if Dourson or Crump were to write a short position paper and send it to the reviewers, a positive consensus would be reached.

IV. Route-to-Route Conversion-Pharmacokinetic Approach

A. Up to now, ECAO has used the Stokinger and Woodward approach as the default position.

B. This approach was generally accepted but with sensible restrictions (i.e., long $t_{1/2}$, no first pass effect, etc.)

C. No major obstacles to consensus.

D. No other comments.

V. Multiple Chemical Assessment

A. ECAO has not had a formally accepted approach.

B. For carcinogens, there did not seem to be any serious problem with using response addition with $r = o$. For toxicants, I was surprised by the problem that a minority of reviewers had with the dose addition approach. This conservative approach is the only reasonable way to avoid presenting results as a vector.

C. What problems arose were at least partially attributable to a lack of familiarity with the literature.

D. I have no problem with the vector approach - it more clearly reflects the complexity of the issue. I also have no problem with summing the vector. It is reasonably conservative and a defensible default position. Many of the problems could be avoided if EPA adopted a quantitative dose/response approach for toxicants - something which is reasonable and which I have long advocated. It would, however, take some development.

VI. Mathematic Models - Mechanisms of Toxicity

I will not give a detailed response to this presentation because Dr. O'Flaherty did not have sufficient time to develop her topic. Her short discussion of the first pass effect was lucid and instructive but elementary. Dr. Hertzberg's introductory remarks set an excellent tone for the discussion which was not given adequate time.

VII. Approaches Using Structure-Activity Relationships

A. Dr. Enslein gave a good overview of QSAR approaches but I wish he had been more specific. He has considerable expertise in this area and I think that the group would have profited from a more detailed discussion. Dr. Broderius's discussion of Duluth's QSAR and joint action work was fascinating but the connection to human risk assessment could have been more clearly indicated.

B. No consensus on the application of QSAR was reached.

C. This entire field requires much more validation before it can play a major role in human risk assessment.

VIII. Use of Reproductive Effects as Endpoints in Risk Assessment

A. Dr. Manson gave an extraordinarily lucid and instructive presentation. Given the limited experimental experience of the group in developmental toxicology, her case study approach was very useful.

B. No consensus was reached on specific or unique approaches for reproductive effects.

C. I hope that Dr. Manson's participation continues. As we become better able to utilize her expertise and as she comes to better understand the goal of and problems in risk assessment, I think that her interaction with the methodology group could be extremely productive.

NEW TOPICS - These all involve tasks on which I am currently working for ECAO. I will be preparing very detailed reports which preclude the need for detailed comments in this memo and I will await reports on the two workshops which I did not attend.

cc: J. Stara
M. Dourson
C. Beigh

PRD:slh

POST-MEETING MEMORANDUM

EPA-ECAO 12-13 July 1983, Cincinatti, Ohio.

1. Hertzberg discussion re model building and testing. I would like to point out that there is circularity in the procedure of testing an equation with a new data set. This circularity applies to any model-building effort, and is not limited to this particular instance.

The probelm is that when one tries to evaluate a model with a new data set one specifies that the test data must not be outside of the space spanned by the design data. This is another way of saying that the test set is homogeneous with the design set. Then, unless there are sampling problems, it is inevitable that the results obtained with the test set will mimic those obtained from the design set. Unfortunately, there is no escape from this problem.

2. Route-to-route transformation. This would appear to be a prime opportunity for the application of structure-activity concepts. What would be needed is data for the compounds from which the model would be devised for both routes of administration, for a sufficient number of chemicals. It would seem likely that such data exist, for example, for rat oral LD_{50} and inhalation LC_{50}. We have in fact collected such data and believe a model could be constructed. I again would also like to point out that similar principles exist between any pair of endpoints for which the data exist, whether thay be obtained by different routes, in the same or different species, etc.

3. Dermal toxicity. Several times the topic of dermal toxicity arose. I would like to point out that vast amounts of dermal toxicity data exist in the literature, and that it would also be practical to develop a model which would relate dermal endpoints to other endpoints, such a oral and inhalation.

4. Mixtures. After I gave my presentation, it occured to me that the molecular-orbital calculation methods that Paul Seybold has been using might be applicable to mixtures. Suppose one considers that a mixture is a jumble ,or juxtaposition of a number of molecules. then it is conceivable that one could calculate the interacting forces between these molecules, and estimate the total effect. It probably would be necessary to take into account the receptor(s) involved, but that too would seem to be practical, given interactive graphical methods. I will discuss the possibility with Seybold, and will also keep it in mind at the Gordon Research conference on the topic , which will be held beginning 25 July.

Kurt Enslein
14 July 1983

Rolf Hartung, Ph.D.
Consultant in Environmental Toxicology
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POST-MEETING MEMORANDUM

July 20, 1983

Dr. Cipriano Cueto
Dynamac Corporation
11140 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Cueto:

The EPA Methodology meetings on July 12 - 13 in Cincinnati generated several new ideas which should serve to improve the risk assessment methodology. However, because of the size of the meeting, complete consensus was rarely achieved on any of the issues discussed. If one considers that many aspects of risk assessments must rely on extrapolations which are based on "reasonable or plausible hypotheses" which have not been verified, then such a lack of consensus is understandable. In my opinion, it is more valuable to explore the range of alternative hypotheses and their assumptions, than to seek consensus. I abhor the idea of establishing consensus by majority vote.

Many of the methodological aspects which were discussed had been wrestled with previously. I fear that some of the methods may be accepted just because they have been reiterated often enough, and because there is simultaneously a lack of data to support or to refute a specific method.

I would like to discuss specifically several methods which seem to have those characteristics.

Exposures to Multiple Chemicals:

This has been one of the major themes during the recent methodology meetings. The topic is obviously very relevant and very important for the evaluation of risks from exposures in the "real world". Discussions of the most plausible extrapolation models for the evaluation of multiple chemical exposures invariably settle on the various additivity models. What is not fully discussed is that all of the data on additivity which have been found useable to explore the phenomenon have been gathered for high dose exposures, and a majority have been derived from single dose exposures. Almost all of the exposures have been to two chemicals only. Such combinations of factors are likely associated with nonlinear kinetics. Whether "additivity as a rule" predominates for chronic low level exposures to multiple chemicals is completely speculative at this time, and all of the modelling and arguing in the world will not alter that status. We simply need to do research to find out what is happening! By identifying this research need, I do not propose a proliferation of acute studies which seek as the main goal the biochemical basis for specific two-chemical interactions. The basic need is to do chronic multiple chemical exposures near previously identified LOAEL doses using protocols which can be used to test various interaction models.

Low-Dose/Long-Term Extrapolations for Carcinogens: I note less and less in-depth discussion concerning the currently accepted modification of the multi-stage extrapolation model. The discussion of less-than life-time exposures to carcinogens revolving around early-stage vs. late-stage carcinogens appears to imply that the coefficients in the exponential polynomial which constitute the multi-stage model, have real biological meaning. Every study of various mathematical dose-response models used for very low risk extrapolations has demonstrated drastic divergence between models for very levels of risk. While attempts have been made to justify the exclusive "scientific validity" of the multi-stage model, such attempts do not do justice to the actual scientific uncertainties which are involved. Issues related to the degree of conservatism in the selection of extrapolation models incorporate personal and/or political value judgements which should be considered issues separate from scientific uncertainty pertaining to accuracy and precision of the extrapolations.

Species to Species Extrapolations: This is an area of continuing controversy and active discussion. That is probably because this type of extrapolation appears to be susceptible to better resolution through research by employing pharmacokinetic and pharmacodynamic techniques, studies of metabolism and of macro-molecular binding in relation to measured adverse effects. Various forms of such research are being actively pursued in many institutions, but many of the research protocols do not seem to be constructed with a consideration of an ultimate end-use related to the species: species extrapolation problem. The species differences due to excretion rates and residence times in the body were specific issues which had not been that thoroughly considered in previous meetings. These issues require further elaboration. That can be done more readily by a small task-group rather than a large committee. At this time it is clear that a simple cube root conversion may be useful as a default condition, but there seem to be many conditions when that conversion does not apply. The influence of metabolic activation vs. inactivation in relation to the cube root conversion was brought up again, but once more there was insufficient time and effort focussed on that issue. In the overall scheme of things these species:species extrapolations should take the place of the arbitrary 10X safety factor traditionally employed for species differences in setting A.D.I. levels.

Multiple-Route Exposures: the evaluation of multiple route exposures was analyzed as a special case of route:route extrapolation, and in the case when exposures by different routes produced different effects as a special case of multi-chemical exposure. The simplistic additive approach suggested earlier, and as summarized in the pre-meeting information, was considered to be inadequate.

The approach taken to the problem was to consider first those conditions under which a multi-route exposure evaluation could be made with confidence. In order to keep the problem tractable, the problem analysis was considered for a single species only. An evaluation with confidence can be made if and only if all of the following conditions are met:

1.- the dose-duration of exposure patterns are identical for all routes of exposure;

2.- the systemic effects are identical for all routes of exposure;

3.- no route-specific effects are found at the portal of entry;

4.- there are no first pass effects;

5.- the dose-duration of exposure-response surface is known in terms of absorbed dose (or: the relationships between applied dose and absorbed dose are known for each route).

Points 1 and 4 are likely to become unimportant if the chemical is cleared very slowly from the body.

If all of these conditions are met, then the total absorbed dose could be estimated, and subsequently the systemic response in terms of absorbed dose could be evaluated.

It was recognized that these preconditions would only rarely, if ever, be met for a specific compound. It was also pointed out, that as these various pre-conditions are violated, then the ability to predict the consequences of exposures by various routes deteriorates in ways that are not easily predictable.

If there were route-specific effects, then a simple summation of absorbed doses would probably be misleading, since interactions between effects would not be taken into account appropriately. Under such conditions (if dose/response relationships were known for each route of exposure), the problem could be treated as a special case of the simple joint action additivity model as postulated by Bliss(1939). Such a model could readily be formulated in terms of external dose, rather than absorbed dose.

Since exposures by multiple routes appear to be common, and since dose/response information is often imperfectly known for the various routes of exposure, it is tempting to attempt estimations of the effects of multi-route exposures on the basis of mixtures of chronic and acute data or on the basis of chronic data alone. Such estimates may be very unreliable and misleading.

Overall, I judged the meeting to be productive. However, a number of the issues which were raised in the meeting could not be adequately considered because of time constraints and because of the number of participants involved. Such issues should be handled is smaller groups with smaller agendas.

I hope that you find this information useful.

Sincerely,

Rolf Hartung

MIT E40-239
[illegible]

(617) 253-6468

July 23, 1983

Cipriano Cueto, Ph.D., Program Manager
Dynamac Corporation
Enviro Control Division
The Dynamac Building
11140 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Cueto:

I very much enjoyed the opportunity to participate in the recent EPA risk assessment meeting on July 12-13. Please feel free to call on me again if I can be of help in the future. Enclosed are my post-meeting memorandum, expense form, and receipts.

Sincerely,

Dale Hattis, Ph.D.

July 23, 1983

To: Cipriano Cueto, Ph.D.

From: Dale Hattis, Ph.D.

Re: Postmeeting Memorandum for Workshop on Risk Assessment Methodology

I. Interspecies Conversion of Dose and Duration of Exposure for Non-Cancer Effects

The most common approaches at present in risk analyses by EPA and others are options number 1 and 2, as outlined in the pre-meeting briefing paper--simple mg/kg body weight or mg/body surface area conversions. The major EPA proposals were to modify these based on either

(option 4) pharmacokinetics of the chemical, including activation or detoxification, and

(option 5) goodness-of-fit to the toxicity data

Both of these have their merits. If sufficient cross-species toxicity data is available, option 5 is clearly to be preferred, as it would implicitly account for both pharmacokinetic differences and any differences related to the receptor(s) for toxic effects. If good cross-species toxicity data is not available, but some cross-species pharmacokinetic information can be obtained, then option 4 should generally provide the best guidance. In both cases, however, the choices should not be limited to simple mg/kg or mg/surface area rules, but should allow for a gradation of body weight^n scaling factors, as indicated by the available information (see further discussion below).

Option 3 (mg/kg brain weight for CNS effects or, by extension mg/target organ weight for other effects) may have been constructed on the premise that one should expect effects in a target organ to be similar across species for doses of chemical that produce similar concentrations of active chemical in the target organ. This is a reasonable premise. However, the concentration of active chemical in the target organ will generally depend on the total body distribution and metabolism of the chemical, not simply the volume or weight of the target organ. Therefore option 3 is unlikely to improve the accuracy of dose rate projections except in the rare case where the great bulk of the chemical is distributed to the brain (or other target organ).

Most of the discussion in the workshop centered on what general rule(s) should be adopted in the usual case where one does not have good cross-species chemical-specific pharmacokinetic or toxicity information. Based on experience with biological half lives of methyl mercury and various drugs, there appeared to be general agreement that mg/surface area dose conversion would more often be a more accurate predictor of internal body (dose X time) of active chemical than simple mg/kg body weight conversion.

There was considerable interest, however, in a paper I brought to the attention of the group (Boxenbaum, H.: "Interspecies scaling, allometry, physiological time, and the ground plan of pharmacokinetics." J. Pharmacokinetics and Biopharmaceutics 10 201-227, 1982). A major thrust of this paper is that basic metabolic rates in organisms scale to (body weight)$^{.75}$. Therefore the turnover time of the average body constituent is proportional to

$(\text{body weight})^{1}/(\text{body weight})^{.75} = (\text{body weight})^{.25}$

Boxenbaum assembled data which indicated that in general the interspecies scaling of biological half lives of drugs tended to cluster around this same value, although the caveats must be attached that

- o there were considerable departures for individual drugs (ranging from body weight exponents of .06 to .428 for the eight examples listed), and
- o in three of the eight cases, the data for humans were considered an outlier from the general pattern and were excluded from the analysis

I think that useful insights might be obtained by assembling more of this kind of information, and attempting to discern patterns in (1) which kinds of chemicals scale with larger vs. smaller body weight exponents, and (2) which kinds of chemicals appear to give rise to anomalous human data; in which direction is the data anomalous (toward more persistence/greater risk or toward less persistence/lesser risk) and how large is it? In the absense of other information, I think that mg/kg doses of chemicals should probably be scaled by a (body weight)$^{.25}$ factor rather than the (body weight)$^{1/3}$ which corresponds to the surface area conversion or the (body weight)^{0} which results from the simple mg/kg body weight procedure.

There was not much discussion of the propriety of fraction-of-lifespan scaling of duration of dosage for non-cancer effects. It is difficult to entirely separate consideration of dose duration from the dose rate problem discussed above. In the absense of other information, lifespan scaling seems reasonable. However, I would think one could place the assumption on firmer footing if at least a limited number of comparisons could be made of the time X dose-rate tradeoff for a few defined toxic endpoints (e.g. LD50, x% impairment of some neurological function) for a few species with differing lifespans. If the dosing-time increase needed to halve the required dose to produce several different endpoints really were directly proportional to lifespan in the model systems, this would support use of the proposed rule.

II. Health Risk Assessment for Less than Lifetime Exposure

Toxicants

The two options outlined in the briefing package do not differ much. Essentially, option 1 calls for a grouping of the data into four discrete time-lengths of exposure, and option 2 contemplates use of ungrouped data to estimate a line for any duration. Given a choice, I would think that the procedure using ungrouped data is slightly better in that it uses all the available information in a systematic and non-arbitrary way (grouping tends to sacrifice some information).

I do not recall very much explicit discussion of the differences between these options by participants in the workshop. I remember that I expressed some reservations about the adequacy of the 10-fold safety factor for within-species and surface-area-converted data (see discussion of hypersusceptibility issue below) and others may have shared this concern.

Carcinogens

The presentation by Crump of the results of his calculations under the multistage model (option 3) was quite cogent, although some present may have had some difficulty grappling with the technical details of the modeling. Crump's approach has clear theoretical superiority to the present procedure (option 1) of ignoring the expected age differences in cancer dose-effect relationships. There is, of course, the considerable practical difficulty of deciding whether one is dealing with an early-stage or a late-stage carcinogen in specific cases, and deciding exactly how many stages to assume. These uncertainties, however, can be explored with sensitivity analyses and presented as part of the overall uncertainty of quantitative carcinogenesis risk projections. I heard no serious explanation or advocacy of option 2, and I think it is preferable to base projections of risk on models (like Crump's) that are firmly rooted in some sort of hypothesized mechanisms for the effects being studied.

III. ADI's Based on Quantal, Continuous or Graded Data

The options here were basically

1. Fit a mathematical model to the animal dose response data as in carcinogenesis risk assessment and interpolate all the way down to risk levels of concern (10^{-6} or 10^{-7} or so--I think the 10^{-5} suggested in the briefing package is quite high for an acceptable risk level except under unusual circumstances with very clear benefits for risk assumption.)

2. Fit the same kind of models but project down only to some "benchmark" risk level (10^{-1} or so). Beyond that, use "safety factors" to establish ADI's. Safety factors could differ for different kinds of effects depending on the severity of the effect, the quality of the data, and the mechanism of the effect.

I have misgivings about both these approaches, but with current information and some modifications, option 2 is preferable. The fatal difficulty for option 1 is that the steepness of the dose response relationship observed for a classic toxic effect (one that is characterized by individual thresholds for response) depends entirely on the diversity of the exposed population. For example, if the exposed population is relatively uniform, the dose that produces the response in 80% of the exposed individuals might be only 1.5 times the dose that produces the response in 20% of the exposed individuals--making for a very steep dose-response curve. Any mathematical model applied to such dose response data and used to directly project human risks at all dose levels would necessarily incorporate an expectation that this steep kind of relationship would also be seen in humans. One thing that we can be very confident of, however, is that a typical human population exposed to the same agent will be very much more diverse in individual response thresholds than the inbred and age-restricted populations of experimental animals that are used for testing. In general, therefore we must expect that the population dose-response relationship in people would be much shallower--and carry relatively greater risks at low doses--than would be expected if people were as uniform in their response thresholds as the test animals. There is just no way to get appropriate information about the distribution of human response thresholds directly from the animal data that will be available in most cases.

The (option 2) approach of modeling down to a selected (relatively high) risk level and applying a "safety" factor is objectionable in that it mixes a finite/quantitative risk assessment approach with the more traditional tool of determining a dose thought to pose no risk by applying some standard rule of thumb beyond the level where data is available. In view of the difficulties of full quantitative risk assessment alluded to above, however, it is probably the best that can be done for most chemicals at present. However, with the majority of the people in the hypersusceptibility work group, I would suggest that different "safety" factors should be used for different kinds of effects, depending on

- o The likely bredth of the distribution of susceptibility in the exposed human population for different chemicals and effects (I presented a detailed outline for work in this area during the hypersusceptibility study session)

- o Policy judgements about the severity and socially desirable protective posture for different kinds of effects.

In this context, as a technical matter I don't like the use of the terms "safety" or "no-effect level" because these imply population thresholds and zero risk. As Dr. Crump pointed out, his modeling approach to compute a benchmark exposure level from the animal data that gives rise to a defined proportion of response in the target population should not be portrayed as calculating a level at which one expects no (zero) animals to show the response. The "no effect" levels ususally determined depend simply on the size of the population of animals studied and the bredth of the distribution of individual thresholds in that population. Similarly if the computed benchmark levels are used to calculate ADI's using "safety" factors there is an unfortunate implication that the calculated ADI represents a level of exposure which should produce absolutely no risk in the human population. In fact, however, if the chemical worsens some physiological function that in some people is already below levels necessary for normal functioning (e.g. oxygen transport to the heart muscle in people with agnina pectoris) then in prinicple there can be no threshold of exposure below which no people will be adversely affected.

IV. Route to Route Conversion

The presentations in this area at the meeting were excellent and, as I remember, evoked no serious dissent. The proposed consensus approaches in areas B (conditons acceptable for extrapolation) and C (extrapolation procedures) in the pre-meeting briefing package also seem quite reasonable as stated. I would add only a modest qualification to A (exposure routes) to the effect that while dermal absorption is indeed negligible as a route of exposure in most general environmental contamination situations, it sometimes is important when evaluating exposures from chemical products within the province of the Toxic Substances Control Act and the Consumer Product Safety Act (e.g. lubricating oil additives, household window/wall cleansers, dyes used in inks, chemicals used in photographic development and copying machines). People in the Office of Toxic Substances have considered dermal absorption important enough to fund the compilation of a data base on dermal absorption kinetics and toxic effects from chemicalls administered dermally within the SPHERE component of CIS.

V. Multiple Chemical Assessments

The options here are either to essentially ignore the presense of multiple chemicals (choosing only the single chemical of greatest concern--option 1) or to construct some kind of index designed to be proportional to the overall level of concern one might have if the risks posed by all the chemicals present simply summed up to a total risk (option 2). Although there was vigorous dispute in the meeting as to the propriety of a simple additive index of concern crossing diverse kinds of chemicals and toxic effects, I think this is an eminently reasonable quick-and-dirty approach for general screening/priority setting purposes. It may not be the way one would go about a detailed full-dress quantitative assessment of the risks of an exposed population if one really wanted to know how many people are likely to be hurt to the greatest accuracy possible with available information. However, if the need is to approximately rank for attention some large number of waste sites with many chemicals per site and huge uncertainties as to the nature and extent of exposures, no better than a quick-and-dirty approach is feasible or reasonable within the constraints of time and information available to make real choices.

VI. Hypersusceptibility Workshop

There was substantial agreement by the participants in this workshop that getting some kind of quantitative handle on variation in susceptibility in the human population was an important area of research for improvement of current EPA risk assessment practices. In general it was felt that this kind of consideration should be built into the calculation of ADI's, rather than (as suggested in pre-meeting material) incorporated as an add-on to estimates of populations at risk. There seemed to be good agreement that in calculating ADI's different safety factors should be used for different kinds of adverse effects depending on (1) the likely population distribution of sensitivity for the effect in exposed humans and (2) policy judgements as to the degree of protection desirable (i.e. "acceptable" risk levels) for specific effects.

As part of the workshop, I outlined an approach for research and modeling to define distributions of susceptibility for "classic" toxic effects (those with thresholds). Enclosed is a copy of this outline. Some in the group felt it would be more important to define distributions of susceptibility for kinds of effects without thresholds (e.g. cancer and also "chronic cumulative" effects by my taxonomy). I think the issue is important in the latter cases, but is the main determinant of quantitative human risk for the threshold-type effects. Prior to the meeting, I provided to Dr. Erdreich a copy of a proposal I submitted some time ago to NIOSH to compile information on the human variability of parameters likely to produce differences in susceptibility to carcinogens. I would welcome an opportunity to do further work on this subject for all kinds of adverse effects.

VII. Exposure Workshop

The main item of consensus to come out of this meeting was that there should probably be more interaction between the groups estimating exposures and the groups calculating dose response relationships and numbers of people affected in normal EPA risk assessments. Without interaction, there is a substantial chance that the the exposure group will not provide information to the risk assessors integrated in appropriate time intervals (in the light of the expected dynamics of production of the adverse effects) or subdivided by the population groups that may differ systematically in dose-response. There is also some chance that the risk assessors could simplify the task of the exposure estimators by advising on the chemicals (or "marker" proxy exposures) of greatest interest for measurements and modeling.

Dale Hattis*
7/13/83

Comments on the Treatment of "Hypersusceptibility" in Risk Analyses for Non-Carcinogens

1. Subject should be considered central to the projection of risk for types of effects that occur when a stimulus overwhelms some specific body compensatory processes (i.e. not information-change type mechanism or accumulation of small irreversible damage steps).

    --framework of traditional toxicology: probit analysis presumes log normal distribution of thresholds

    --importance in past rulemakings

    - o carbon monoxide/angina sufferers
    - o lead/children with pica/children at risk for mental impairment
    - o asthma sufferers/sulfur oxide standard

2. Comments on the proposed approach for considering "hypersusceptibility" in agency risk assessments.

    --the proposed approach assumes a discontinuous-population-subgroup model of "hypersusceptibility"; however much of the variability between individuals in susceptibility may appear as continuous due to a host of factors acting as quantitative characters, and not based on obviously discernable membership of people in discrete, countable subgroups.

    --the proposed approach appears to implicitly assume that the average "hypersusceptible" person is only about twice a susceptible as the average non-"hypersusceptible". (If the difference were really to be as small as this, it wouldn't be worth much bother amid the other uncertainties of quantitative risk assessment.)

    --the propsed restriction to "hypersusceptible" groups comprising at least 1% of the population, while it flows naturally from the propsed calculation method, is arbitrary and potentially seriously misleading. Consider, for example, a case where there exists a .1% subgroup that is ten thousand times as susceptible to a toxin as the average individual. Quantifying the size of the population that is very much more susceptible than average is the essence of a quantitative risk assessment for a threshold character with widely varying sensitivity.

---

*M.I.T. Center for Policy Alternatives

3. Possible analysis of different sources of variation in susceptibility

--exposure is effectively more for the subgroup because of either biology or behavior

o children probably eat more dirt than adults, and children with pica eat particularly more

o children tend to play on old fields more than adults, some of which used to be toxic waste dumps

o children simply breathe and eat more per body weight than adults, even discounting behavioral differences that relate to what they eat

NOTE: THESE TYPES OF DIFFERENCES ARE NOT GREATLY DIFFERENT FOR DIFFERENT KINDS OF CHEMICALS--DATA OBTAINABLE BY POPULATION INTERVIEW/MEASUREMENT SURVEYS FOR CHEMICAL-EXPOSING BEHAVIORS

--parameters determining normal/abnormal function are closer to (or even beyond) the boundary of abnormality for the subgroup. Two kinds:

o disease-based--angina/oxygen deprivation (even more extreme case is people in the process of having a myocardial infarction)

o other interacting exposure--smokers/prior CO exposure ties up hemoglobin that would otherwise be available, thus probably making them more susceptible to the effects of aromatic amines causing methemoglobinemia--not because the aromatic amine ties up any more hemoglobin, but because they have less "reserve capacity" to begin with

INFORMATION ON THESE TYPES OF VARIATIONS MAY OFTEN BE OBTAINABLE FROM CROSS-SECTIONAL INTERIEW SURVEYS OF THE TARGET POPULATION FOR THE PREVALENCE OF RELEVANT CONDITIONS AND POTENTIALLY INTERACTING EXPOSURES. THE RELEVANT CONDITIONS, HOWEVER, WILL VARY FROM AFFECTED-PARAMETER TO AFFECTED-PARAMETER THUS ANALYSIS OF THIS KIND OF VARIATION MUST BE SPECIFIC TO THE PARAMETER, THOUGH NOT NECESSARILY TO THE CHEMICAL. DIFFICULTY: IN MANY CASES THE PRECISE BIOCHEMICAL DISTURBANCE TO HOMEOSTASIS WILL NOT HAVE BEEN DEFINED FOR SPECIFIC CHEMICALS CAUSING CHRONIC TOXIC EFFECTS.

--there is more parameter change/unit dose of chemical for the subgroup, because of biological differences in

o pharmacokinetic factors

the absorption of the chemical (fraction of the amount taken into the lungs or the GI tract that finds its way to the blood stream) the persistence of the chemical or its active metabolites in the body (half-life or more complex parameters of decline with time)

- the fraction of the chemical that is metabolized via active/dangerous vs. inactive/safe metabolic pathways

- factors related to the receptor for toxic action

  affinity of receptors for the toxic agent, vs the affinity for natural competitors (e.g. the affinity of acetylcholinesterase for cholinesterase inhibitor toxins, vs affinity for the natural substrate acetylcholine)

  number of receptors, in relation to the minimal number required for normal function (i.e. the functional reserve at the micro level)

INFORMATION ON THESE FACTORS WILL NOT GENERALLY BE OBTAINABLE FROM CROSS-SECTIONAL INTERVIEW SURVEYS. ANALYSES MUST BE BASED ON EITHER

--CLINICAL OBSERVATIONS OF THE RESULTS OF MODEL EXPOSURES TO THE CHEMICAL UNDER STUDY OR PHARMACOLOGICAL ANALOGUES,

--OR (WITH CONSIDERABLE DIFFICULTY) PROJECTIONS FROM ANIMAL STUDIES.

Suggestion: Divide susceptibility/variability analyses up into these three components.

--Have a reasonably standardized analysis of susceptibility for the exposure-related factors, depending only on the routes of anticipated exposure to the target population.

--Do a series of standard analyses of population variability for different well-characterized physiological functions that are affected by toxic agents (e.g. oxygen transport, nerve conduction). For substances that affect unknown physiological parameters, use a "typical" variability profile borrowed from one of the well-characterized functions for "best estimate" calculations, and some more extreme assumption of variability for "conservative" or "worst case" projections.

--To the extent possible, analyse pharmacokinetic and receptor-related variability chemical-by-chemical. Where chemical-specific data is not available, it may often be necessary to adopt some general rules based on previous experience with specific chemical classes or chemicals affecting specific receptors.

Based on this three-tiered analysis, construct a stochastic simulation model (combining randomly-selected values for each of the relevant susceptibility factors within the three tiers) to compute the overall distribution of population sensitivity for the chemical.

THE UNIVERSITY OF TEXAS MEDICAL BRANCH
GALVESTON, TEXAS 77550

Department of Preventive Medicine and Community Health
Division of Environmental Toxicology
Phone: 409-761-1803

July 15, 1983

Cipriano Cueto, Ph.D.
Project Director
Dynamac Corporation
The Dynamac Bldg.
11140 Rockville Pike
Rockville, MD 20852

Dear Dr. Cueto:

Re.: EPA's Workshop on Methodology for Risk Assessment for Multi-chemical Exposures, held July 12-13, 1983, Cincinnati, Ohio

I was impressed by the scientific expertise represented in this meeting. I felt that the topics were selected with a great deal of care and the level of presentations were excellent. My basic criticism is that our discussion time was so severely limited. This was especially so in our individual workshop sessions. In the session on ranking I was particularly discouraged because a single presentation accounted for almost all of the allotted time. I suspect my adverse reaction was on a very personal level. I had prepared some slides that I hoped would lead to a more productive way of ranking toxic chemicals. Perhaps in a future meeting with a similar number of participants we would be more productive if we were split into smaller groups initially to discuss specific topics.

I will put some of my notes together and send you a more definitive critique at a later date.

Yours truly,

Marvin S. Legator, Ph.D.
Professor and Director

MSL/tml

Postmeeting Memorandum of Jeanne Manson

Session III: B, A2: Ranking the Severity of Effects.

Presentor: P. Durkin

RE: Table 1. Rating Values for Toxic Effects

I am somewhat concerned about the rating score for point #8, which includes the statement "Any decrease in reproductive capacity, any evidence of fetotoxicity". My concern is that these events could occur as secondary or tertiary effects of generalized toxicity, and may not represent the irreversible or significant toxicity implied by the high rating score. In the case of reproductive capacity, transient decreases in sperm count or dysmenorrhea can occur as a result of general systemic toxicity, given that the function of the reproductive system is dependent upon the highly integrated function of a number of other systems. Consequently, I think a distinction should be made between reversible decreases in reproductive capacity versus long-term decreases in reproductive capacity and decreases in reproductive capacity that occur with general systemic toxicity from those occurring in the absence of other types of toxicity. Reversible decreases in reproductive capacity, and/or decreases in reproductive capacity accompanied by general systemic toxicity could be placed under point 7 to reflect detectable decrements in organ function.

A clearer case can be made for underrating "any evidence of fetotoxicity" given the often-quoted rule of Karnofsky's law, which is that any agent can be shown to be teratogenic (fetotoxic) if administered at high enough levels at the appropriate time of gestation. I think if "fetotoxicity" were more specifically defined, then a lot of confusion could be avoided. For example, decreases in fetal body weight and increases in delayed ossification accompanied by maternal toxicity could be placed under point 4. Excessive embryolethality accompanied by maternal toxicity could be placed under point 7. Any teratogenic effect with maternal toxicity could be listed under #8. The most important point, however, is that to leave the statement "any evidence of fetotoxicity" without qualifying whether or not the fetotoxicity occurs at maternally toxic doses is the same as incriminating all compounds tested at maternally toxic doses.

M. A. MEHLMAN
7 BOUVANT DRIVE
PRINCETON, N. J. 08540

July 25, 1983

Dr. C. Cueto
Dynamac Corporation
Enviro Control Division
The Dynamac Building
11140 Rockville Pike
Rockeville, MD 20852

Dear Dr. Cueto:

I would like to comment on the EPA's Workshop on Methodology for Risk Assessment for Multiple Exposures which was held on July 12-13, 1983 in Cincinnati, Ohio.

After a somewhat slow start on July 12, due to prolonged discussion of issues, the Workshop picked up speed on the second day. It was clear that in order to deal with these complex topics, it will be necessary to commission one or two people to develop position papers. Most of the groups that meet in separate sessions have recommended so.

The session that I chaired, The Use of Exposure Data in Health Risk Assessment, has raised concern on the following:

- We assume that the type and amount of wastes will be reasonably well characterized (but may be deficient in some cases).
- Exposure assessments are resource-limited and data-limited, and exposures are variable in space and time; therefore, exposure cannot be characterized by a single number.

The following data are desirable for characterizing exposure:

- Monitoring data from air, water (surface and ground) foodstuffs (especially fish) and soil must be determined to adequately establish the level of substances present.
- Tissue/excreta monitoring in humans or animals from the area is extremenly valuable in assessing exposure.
- Human behavioral observations in the area should be made to identify exposure routes or sensititve individuals.
- Attention should be given to proper locations of monitoring wells.

- The output should be explicit as to the variability associated with exposure, both in space and time.
- Monitoring data and exposure assessements come from a wide variaty of sources within and without EPA. Close communication between those responsible for each phase must be encouraged, especially if a second phase of monitoring can be done.
- We recommend that the Agency commission a paper discussing integration of environmental monitoring, exposure, and health data, including the role of epidemiology of exposure.

This Workshop has accomplished it's goals by thoroughly discussing the state of science of topics that were assigned and by identifying and recommending steps to be taken to deal with these topics.

Sincerely,

M. A. Mehlman

Post meeting coments, W. J. Nicholson

A. Interspecies of conversion of dose.

I would suggest that our understanding of interspecies conversion of dose, at least for some end points such as cancer, is insufficient to allow a specific policy to be established. It would appear that the factor to be utilized depends strongly upon the metabolic processes involved the toxic effect in question. As an example, I would cite the emerging data on the carcinogenicity of vinyl chloride in humans as compared to that in rats. Data from the extensive series of Maltoni suggest that 15% of rats exposed to an air concentration of 250 parts/million (8 hours/day, 5 days/week, 52 weeks - 1/3 of a lifespan) develop hemangiosarcoma of the liver. (note an adjustment to an 8 hr. day)

Data from human epidemiology (Nicholson Proc. Int. Symposium on hazards related to plastics and synthetic elastomers. Helsinki, Nov. 1982). suggested that from 200 to 600 hemangiosarcomas of the liver will eventually occur among U.S. VC-exposed workers from exposures that occurred prior to 1975. These cancers will occur among approximately 5000 workers exposed in the industry to 200-500ppm for periods from 10 to 40 years (approximately 2/7 of a lifetime). Thus the equivalent human risk is 4% to 12% over the remaining lifespan of the workers.

One can assume that man inhales 40 times more VC (Scaling as 2/3 - oxygen consumption scales as $W^{2/3}$. If the risk of HSA in the liver is proportional to the VC concentration, then the concentration in man is $\left(\frac{W_m}{W_r}\right)^{-1}$ less than the rat (if all VC inhaled is metabolized). This suggests that for the same air concentration, the time concentration will be $\left(\frac{W_m}{W_r}\right)^{1/3}$ or 6.5 times more in the rat than in man. The observed risk in rats appears to be 1 to 4 times greater--a reasonable agreement considering all the uncertainties.

The above, however, completely neglected the species dependence of activation. Gehring et all have explained the observed non-linear dose response function for Maltoni's experiments in terms of Michaelis-Menten kinetics in which the maximum rate of conversion of vinyl chloride to the reactive epoxide is 5706 migrograms/4 hours. It is not know whether similar Michaelis-Menten constants will apply in man. If they are significantly different, the concentration of ractive metabolite in the liver will differ from the naive estimate above.

If the kinetics (constants in Michaelis-Menten equation) of metabolic activation are species dependent, significantly different species conversion factors would obtain depending on whether a carcinogen is direct acting (and metabolism reactivates) or requires activiation.

B. Procedure for estimating risk for fraction of a lifetime exposure

The multistage model proposed by Crump and Howe would appear to be eminently suitable for estimating lifetime-risk for less than lifetime exposure for most carcinogens. However, the mode of action of a carcinogen must be carefully considered as different less than lifetime risks would be estimated depending upon whether material is acting predominantly as an initiator, (early stage carcinogen) or a promotor (late stage carcinogen). Thus, as with interspecies conversion, knowledge of the mechanism of action, material is important in the application of a model.

The procedure for estimating a risk for less than lifetime exposure for non-carcinogenic effects can be established easily if the procedure discussed for calculating a pseudo NOEL or 1% NOEL become generally utilized. The less than lifetime dose can be quantitatively established by considering the calculated 1% NOELs established at different fractions of a lifetime. A regression line utilizing these values can be calculated with each value being weighted by the reciprocal of the calculated variance of the 1% NOEL level. This procedure can of course work only if there are sufficient data available in each discrete fraction of a lifespan period.

C. ADI's based on quantal, continuous or graded data

Whenever possible, continuous data should be utilized for estimates of biological effects rather than quantal data. For example, the average weight loss of a group of animals to a given concentration give a far more accurate measure of effect than the percentage of animals that are below some specified "normal" level. Such continuous data could be incorporated into a model (Probit, linear, etc.) in which a 1% effect is calculated. With such a calculated 1% effect, an uncertainty factor could be established for regulatory purposes.

D. Safety factors

Much more data are required for the establishement of safety factors. Currently, a factor of 10 is utilized to account for variability within species (man). This may not be at all adquate considering the special sensitifity of children, often coupled with greater exposure to toxic environmental agents.

One useful set of data on intraspecies variability would be to look at the variability of biological sensitivity to some agent in a purebred strain of animals and in a variety of inbred strains of the same animal. It would then be possible to calculate the difference in doses for an effect at the 0.00 1% level that would be estimated from measured effects at much higher doses.

Clement Associates, Inc.
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August 25, 1983

MEMORANDUM

TO: Jerry Stara, ECAO, USEPA, Cincinnati, Ohio

FROM: Ian Nisbet, Clement Associates, Inc., Arlington, Virginia

THROUGH: Christopher Dippel, Dynamac Corporation, Rockville, Maryland

RE: Post-Meeting Memorandum, Workshop of July 12-13, 1983

General Comments

I found the workshop helpful and stimulating, and I appreciated the opportunity to take part in it. I felt that too much time was spent in recapitulating old topics and bringing new workshop participants to the point reached at the end of the last meeting. On some of the old topics (e.g., interactions) we did not even reach that point. For this reason, we did not have enough time to get far into new topics. Kenny Crump's working paper on less-than-lifetime exposure was very helpful. By contrast, we needed stronger working papers on other topics, such as interspecies conversion of dose and reproductive toxicology.

I think it is over-optimistic to expect to reach "consensus" on topics at or beyond the frontiers of research, such as multichemical assessment. I understand that ECAO has to adopt a set of procedures and needs support from the leaders of the scientific community. Nevertheless, several scientists at the workshop expressed "scientific" caution in making generalizations. I would have liked to see some informal voting on some topics, with the scientists being required to vote for one procedure and not being allowed to avoid expressing a preference by abstaining from voting.

Interspecies Conversion of Dose and Duration of Exposure

The discussion of interspecies conversion of dose was chaotic because several participants failed to define their units. Thus, some participants referred to a dependence on two-thirds power of weight, while others referred to a dependence on one-third power of weight. Both mean the same thing, because the first is appropriate when applied to dose in mg, and the second is appropriate when applied to dose in mg/kg. Before consensus is reached, I think that ECAO will have to commission a well-thought out paper by someone who really understands the mathematics of allometric relationships (few, if any, of the speakers appeared to do so). In the meantime, I would vote for a general assumption that the effective dose in mg/kg scales as the one-third power of body weight.

As I tried to point out, scaling in proportion to ppm in the diet is only appropriate if diets of all species are comparable (all dry weight or all wet weight, not a mixture of both). No one seems to know the dry weight of a human diet.

The discussion of conversion of dose for duration of exposure seemed confused. Scaling duration in proportion to species lifetime seems appropriate for carcinogenesis, but not for other toxic effects. I am not convinced that a 90-day exposure of a rodent is equivalent to a 9-year exposure in humans. For acute, subacute, and subchronic exposures, I would vote for scaling in proportion to biological half-life, but I am not sure this is independent to the scaling in proportion to $W^{-0.33}$, since both reflect differences in metabolic rate. I think that more empirical information is needed, both for humans and animals.

Health Risk Assessment for Less Than Lifetime Exposure

I liked the paper and presentation by Crump, which makes a lot more sense than scaling in proportion to cumulative exposure. I have already been using essentially the same formulas (based on papers by Whittenmore and Day & Brown) for carcinogenic risk assessment.

For noncarcinogenic effects, I think the empirical approach exemplified by the chart for methoxychlor is appropriate, but I think this needs more work. Kenny Crump and I undertook to work on statistical approaches to analyzing such data.

ADIs Based on Quantal, Continuous, or Graded Data

QCG data can always be converted to dichotomous data by setting a more or less arbitrary criterion for the level at which a change becomes an "adverse effect." However, this throws away a lot of information available in the original data.

For truly QCG data, I think the concept of ADI is inappropriate, since such data can often be fitted to nonthreshold models. As for dichotomous data, most toxicologists are conceptually confused between intra-individual and inter-individual contributions to the dose-response curve. When inter-individual variability is substantial, the "equivalent background" or "dose-additivity" concepts invalidate the assumption of thresholds. We need better thought-out models.

Route-to-Route Conversion

I thought we approached consensus that systemic dose was an appropriate method of conversion for systemic effects, but that no method of conversion was appropriate for effects at the site of first contact.

Multiple Chemical Assessment

I don't think we got any further with this difficult topic than we did at the last meeting. At that meeting, I was almost convinced by Crump's argument that to first order, doses of different chemicals should be additive. Dose additivity is the key concept and needs empirical investigation.

Structure-Activity Relationships

I was impressed by Enstein's presentation and regret that there was not enough time for him to explain just what was being analyzed in his multivariate analyses.

Use of Reproductive Effects as Endpoints

I thought Jeanne Manson's presentation was too much concerned with detail and did not approach the topic of whether reproductive toxicity data can be used for risk assessment. I strongly disagree with her implied negative on this question. I recently published a book on this topic (I.C.T. Nisbet and N.J. Karch, Chemical Hazards to Human Reproduction, Noyes Data

Corp., 1983) in which we explored the concordance between human and animal data for the same chemical and cautiously concluded that a semi-quantitative concordance exists if one can identify the appropriate animal species. A copy of the summary of this study is enclosed.

Use and Biological Justification of Mathematical Models

I don't think we progressed significantly on this topic.

High Risk or Sensitive Subgroups

I think that there is abundant evidence for a wide range of susceptibility within the human population to a number of toxic chemicals. However, I don't think we have many cases where we can assume that the distribution of susceptibilities is bimodal. (If we did, we could no longer assume that a linear dose-response curve is conservative, since a bimodal distribution of susceptibilities implies an S-shaped dose-response curve.) For most effects of concern in the human population (including cancer, reproductive, and neurobehavioral impairment) there is a substantial background frequency, suggesting (but not requiring) the concepts of equivalent background, dose additivity, and linear nonthreshold dose-response relationship. These ideas need thoughtful study for effects other than carcinogenesis.

I made the point that small children are more active, spend more time outdoors, eat more, drink more, and breathe more (per unit body weight), and have some presumptively more sensitive organ systems than adults. Hence, the conventional safety factor of 100 is never sufficient to protect small children, since it includes a factor of only 10 for intraspecific variability in sensitivity.

Use of Exposure Data in Health Risk Assessment

Despite the presentations at the last meeting, most participants at the workshop seemed to think that exposure assessment was a straightforward problem in measurement and modelling, and could be carried out independently of hazard assessment. In the few minutes available for discussion, I tried to point out that exposure assessment is extremely difficult with the limited resources usually available at hazardous waste sites, and usually is the critical factor limiting the accuracy of health risk assessments.

ICTN/mrs
Enclosure

Ellen J. O'Flaherty

Postmeeting Memorandum for
"Risk Assessment of Multichemical Exposures" Meeting,
EPA, Cincinnati, July 12-13, 1983

Consensus Topics

A. Interspecies Conversion of Dose and Duration of Exposure

Consensus: For interspecies conversion of dose, continue with EPA's present procedure in which the ratio of equivalent dose rates in two species is considered to be inversely proportional to the cube root of the ratio of the mean body weights of the two species. However, there seemed to be some feeling that this is a default position; that is, it is reasonable and has some experimental support. but nonetheless our understanding of species equivalence of dose rate is incomplete at present. For duration of exposure, the consensus was to continue to use fraction of lifespan for compounds that produce chronic effects, but that time to development of acute effects may be relatively constant across species.

With regard to interspecies conversion of dose or dose rate, I believe that sufficient information is available in the published literature to enable us to address this question much more systematically than has been done by the EPA to date. Harold Boxenbaum has recently (1982) published an authoritative review of interspecies scaling of pharmacokinetic behavior. This paper would be an excellent starting point for an analysis of information on effects across species. Two questions that need to be addressed specifically are: Should interspecies scaling be carried out differently for short-term (non-steady-state) and for chronic exposure situations? How should interspecies scaling be carried out for compounds that are activated, rather than detoxified, by metabolism?

B. Health Risk Assessment For Less Than Lifetime Exposure

Consensus: For noncarcinogens, continue to develop the dose (mg/kg/d) -duration (fraction of lifespan) plot, working toward incorporation of greater objectivity into the process of determination of NOAEL and ADI lines. For carcinogens, use of the multistage model as proposed by Crump and Howe was endorsed except perhaps for childhood leukemias.

I agree with both positions and have no further comment on this point.

C. ADI's Based on Quantal, Continuous or Graded Data

Consensus Fit the entire data set, whenever a data set exists, to obtain an estimate of something or other.

This consensus was not at all clear. I do not believe that most of the participants had thought through the implications of carrying out this procedure with both continuous and quantal data sets. In fact, my own position on this issue has moderated somewhat since the meetings as I have given it further thought.

The general approach, which is to apply various uncertainty factors to a dose selected on some defined basis, will not be altered. The uncertainty factors used by the EPA not only have a history of successful (i.e., successfully protective) use, but they have also been given a measure of at least empirical respectability. In particular, application of a factor of 10 to account for within-population variability appears to be adequate for most chemicals.

The current procedure for selecting the dose to which the uncertainty factors are to be applied is something of a hybrid. Graded toxicity data are used to establish the presence (often at an unspecified response level) or absence (zero observed response) of an effect in a test group of animals. I have always interpreted the various "effect levels" used by EPA as doses associated with some, perhaps unknown, quantal response or occurrence of the effect. Interpretation of one of the uncertainty factors of 10 as accounting for within-population variability is, thus, logical.

Fitting a quantal response data set with a model so as to utilize all available information thus causes no conceptual difficulty. My preference would bes to calculate a confidence limit on the dose corresponding to a specified low risk, say 10^{-2}, and then to apply the appropriate uncertainty factors. This approach is relatively model-independent.

If the recommended procedure, of fitting all the data points, is applied to a continuous data set, then presumably a confidence limit will be calculated on the dose corresponding to an acceptable meann effect intensity. Translated into the language of quantal response, this means that if the distribution of magnitude of effect intensity among members of the population is approximately normal, the dose corresponding to an acceptable mean effect intensity is also the dose associated with appearance of a magnitude of effect greater than or equal to the mean in about half the population; that is, it is an ED_{50} with respect to the acceptable effect intensity. If the distribution of magnitude of effect intensity among members of the population is significantly different from a normal distribution, then the dose associated with the acceptable mean effect intensity is not an ED_{50}.

To sum up, four distinguishable methods have been used or are proposed, to select the dose to which uncertainty factors are to be applied. These are:

Type of Data	Starting Point for Application of Uncertainty Factors
1. NOAEL or NOEL	Dose associated with zero quantal response in experimental group.
2. LOAEL	Dose associated with a positive quantal response, fraction affected often unknown but may approach 1.0, in experimental group.
3. Fit to quantal (response) data	Dose associated with a low quantal response of arbitrary magnitude, say 10-2.
4. Fit to continuous (effect) data	Dose associated with an acceptable mean effect intensity. Quantal response unknown unless distribution of effect intensities is known, but probably is of the order of 0.5.

If one of the uncertainty factors used by the EPA is to be considered protective for population variability, it must logically be applied to dose-quantal response data. All the current or proposed methods use as starting points doses that can be associated with quantal responses as shown above. However, these quantal responses vary from 0 to 1.0. Selection of uncertainty factors to use with these methods should take this variability into account.

D. Route-to-Route Conversion

Consensus: Route-to-route conversion may be undertaken, if necessary, for compounds with long half-lives and insignificant first-pass effects. However, it was generally agreed that lung-to-gut extrapolation based on a TLV is probably not advisable, since TLV's are likely to have been based on the irritative properties of the chemical rather than on its systemic toxicity.

In general, I am in agreement with this position. However, certain refinements were discussed during the workshop session on multiple route exposures. I include a summary of the conclusions and proposal of that workshop under the workshop heading.

E. Multiple Chemical Assessments

Consensus on this topic was not reached, in my opinion. Most of those present seemed to believe that estimation of a total hazard index, using the principle of dose additivity, is the least unreasonable method to use in the absence of specific information concerning the chemicals' toxicities and interactions. However, some participants, particularly those who were present for the first time, clearly were not comfortable with the idea of estimating total hazard at all.

I agree that estimation of a total hazard index based on dose additivity is the most defensible method at present for evaluating health risk from exposure to a mixture of chemicals. I support this approach for two reasons: (1) it is conservative in that, of the various possible methodologies, it is the method resulting in the largest estimated hazard associated with a mixture of chemicals at known concentrations; and (2) it takes into account a contribution by all toxic chemicals known to be present at the site.

Reliance on a "marker" (most toxic) chemical is of no use in estimation of total hazard unless (and until) it can be shown that the kinds and relative proportions of chemicals present at waste dump sites are reasonably constant across sites. Even then, reliance on a marker chemical for hazard estimation would be risky, since the presence of a large amount of an only moderately toxic chemical could greatly increase the actual total hazard. If a marker were used for hazard estimation, other toxic chemicals probably would not actively be sought at the site. Use of a marker chemical to screen sites for classification and for further study is subject to the same uncertainty; however, use of a marker chemical for initial screening purposes may be justifiable on the basis of speed and ease. If this is done, the possibility that a site judged to be a low-risk site may not in fact be low-risk, must be borne in mind.

Workshop Topics

I attended only the workshop on multiple route exposure. Discussion at this workshop, although it was moving in the direction of consensus, did not lead to a definitive statement by the end of the session. Consequently, Dr. Clarkson, Dr. Pepelko and I, with input from Dr. Hartung, spent the time scheduled for the second workshop session in formulating a summary statement based on the discussion at the multiple-route workshop. My recollection of the key points follows.

Summation across exposure routes is possible in principle. The simplest summation method is

$$d_n = d_1 r_1 + d_2 r_2 + \ldots. + d_i r_i \; ;$$

where d_n = total dose, d_1, d_2, ..., d_i = the doses presented to routes 1, 2,...., i; and r_1, r_2,...., r_i = the fraction absorbed for each route.

The ideal chemical candidate for exposure summation across routes would be one that meets all five of the following criteria, outlined by Dr. Hartung:

1. Internal dose-duration of exposure patterns are identical for all routes of exposure. (Thus, for example, concentration "spikes" in the blood do not occur for one exposure route while smooth buildup to a steady state blood concentration is observed for a second exposure route.)

2. Systemic effects are identical for all routes of exposure. (Systemic effects might not be identical for all routes of exposure if, for example, there were a first-pass effect for one route that produced a metabolite whose toxic effects were different from those of the parent compound.)

3. There are no route-specific effects at the portal of entry.

4. There are no first-pass effects.

5. The relationship between applied dose and dose delivered to the target organ is known. (Internal dose, or dose related to concentrations in the blood, is usually considered to be equivalent to delivered dose. However, it may not be.)

Since the characteristics of few compounds will be known with this degree of completeness, it may be possible to state some generalizations about the extent to which different groups of compounds may meet these criteria:

1. Internal dose-duration patterns are likely not to differ significantly across routes of exposure if the chemical has a long $t_{1/2}$. Concentration cycling around the mean steady-state blood concentration is damped if the compound has a long $t_{1/2}$, so that for such compounds the difference between dose-duration patterns for intermittent-exposure routes and for continuous-exposure routes is minimized. Alternatively, even for compounds with short $t_{1/2}$, if patterns of exposure are roughly comparable the internal dose-duration patterns may also be roughly comparable. For example, exposure through water, although discontinuous, would fall somewhere between continuous exposure by inhalation and administration of the same total daily dose to an animal by single gavage.

2. Although situations in which systemic effects are different for different routes of administration can readily be imagined, we were unable to identify any compounds for which this is true. It may be possible to infer that few chemicals do not meet this criterion.

3. Highly chemically reactive compounds, or compounds with long residence times in the tissue of entry, should be suspect with regard to their potential for causing portal-of-entry effects. However, it cannot be assumed that compounds that are not highly reactive or have short residence times in the tissue of entry will not cause portal-of-entry effects.

4. Compounds with long $t_{1/2}$ are less likely to undergo significant first-pass effects than are compounds with short $t_{1/2}$. Thus, as a result of both considerations 1 and 4, it appears that compounds with long $t_{1/2}$ may be suitable candidates for summation across exposure routes.

The assurance with which summation across exposure routes can be carried out varies both with the nature of the data set(s) on which the summation is based and with what is known about the degree to which the compound meets criteria 1-5.

POSTMEETING MEMORANDUM OF MARVIN SCHNEIDERMANN

This report relating to the EPA-Cincinnati meeting of July 12-13, 1983 consisted of these parts:

1. Comments on the "consensus" portions of the meeting (1st day). (Greatest attention given to IA-. Where issues overlap, they are largely discussed under IA.)

2. Summary of workshop A1 (Sensitive sub-groups)

3. Comments on other workshops

4. Suggestions for future meetings (if any). The signal R→ shows where a specific new recommendation is made.

IA: Interspecies conversion of dose and duration of exposure.

A. There are two major areas that remain to be resolved:

   1. The biological or mechanistic basis for the use of any transformation. The surface-area transformation seems to be somewhat more useful than the mg/kg transformation - despite the finding by Meselson several years ago that for the six chemical carcinogens for which there were satisfactory animal and human dose data, the mg/kg transformation provided the most satisfactory interspecies comparison.

      If the specific toxicity associated with a material is related to the metabolism of that material (as, for example, in "first-pass" effects) then it appears reasonable that the interspecies conversion factors are likely to be effect-specific. That might imply that Meselson is correct for cancer as a toxic response, while the 2/3 power or surface-area transformation is appropriate for some (many?) other toxic effects. This, in turn raises regulatory issues relating to the severity of effects, implying that perhaps the appropriate transformation is the one that yields the lowest "acceptable" dose for the key or crucial (or "swing") toxicity.

   2. The different metabolic rate in children may require a different species-conversion or transformation than for adults. If it is true that children have greater intake (food, air, water) than adults per unit weight and/or per unit surface area, then (if different conversion factors are not appropriate) it is likely that tighter standards may have to be set for childhood as opposed to adulthood exposures. This issue is part of the concerns of workshop A1- high risk sub-groups.

B. Other concerns: combination of "toxicities."

The consideration of multiple exposures (as in toxic waste dump effluents), and the combination of exposures via different media is still unresolved. In particular, it seems to me that a set of intermediate guidelines needs to be set out now (to be revised, as necessary, in the future) on:

a. Multi-media exposures, including when and how combined exposures can (should?) be taken into account, effects of "dominant" exposures, appropriate pharmaco-kinetic effects when known (and how these will get to be known better in the future).

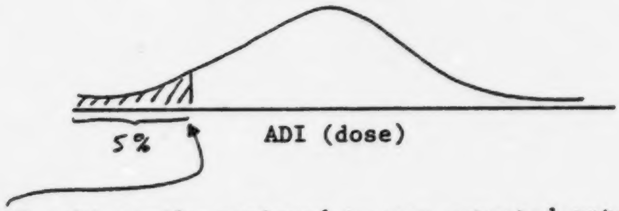
b. Combinations of sub-ADI exposures. (A sophisticated way of handling these may be able to subsume the multi-media exposure problem - if ADI's are, or can be, set up for each route of exposure).

R → At the moment I am inclined to recommend summation of EXPOSURE/ADI for similar (same?) toxic responses, and then either a grand summation across all toxic reponses (which data I doubt exists) or an evaluation of the first stage summation for the key, crucial, dominant, swing toxicity (much of which data will also be missing).

R → A system of "default" penalties for missing data will probably have to be developed. The absence of toxicity data should lead to more rigid standards for exposures in general. (I can conceive of circumstances in which data on a serious toxic effect would make it unnecessary to develop data on a less serious effect, however). Not knowing should carry more of a penalty than knowing. A possible "penalty" system would assign an upper 95% toxicity level (as found in the distribution of all materials that have been tested for the specific toxicity) to any untested material.

e.g.,:

Distribution of ADI's for Toxicity "A"
for all materials tested to date



ADI arbitrarily assigned to any untested material

C. Summary

1. For use until future notice:

a. Surface area transformation

b. ppm (in food, water, etc.): no transformation
(Be concerned about adult-child differences)

c. Same transformation for all toxicities
(Be concerned about adult-child differences)

d. Same transformation for all toxicities
(Be concerned about pharmaco-kinetics)

e. Same transformation (possibly into ppm) for all media

f. Penalize missing data
(develop a system to be presented at a future meeting)

g. Summarize total exposures by

$$\sum_{k} \sum_{j} \sum_{i} \left(\frac{\text{Exposure}}{\text{ADI}} \right)_{ijk}$$

i = materials $1 \ldots n_i$

j = toxicities $1 \ldots n_i$

k = media $1 \ldots n_k$

see text above

2. Research issues (a sampling)
   a. (as indicated above)
   b. Effect of one time exposure
      - spills, in contrast to elution over time from dumps
   c. Effect of changing exposures with time
      - mechanism of toxicity (i.e., relation to cumulative dose? peak dose? etc.)
   d. Differences among materials that need to be
      activated
      materials that are direct-acting
      materials that are inactivated.

Session IB.

Health risk assessment for less than lifetime exposure

A. Mathematical modelling

1. Recognize that few disease-dose models exist for other than cancer. I am not certain that models really need to be developed for all (or even for many) of the non-cancer effects. Models are needed only there is uncertainty about

thresholds and/or the interactions with other exposures producing the same effects (hence the concern about dose additivity vs response additivity). At present I see a possible need for models for chronic disease effects other than (or in addition to) cancer. (For example, for arthritis, emphysema, hypertension, other coronary/circulatory diseases.)

2. Mathematical modelling for cancer is developing greater sophistication. The major missing link that I see is in bringing two major classes of models - the "sensitivity" models (logit, probit, Mantel-Bryan, Weibull, time-to-tumor) and the "mechanism" models (multistage, multi-hit, one hit) together, giving us a mechanism model that also takes sensitivity into account. At present, I find the multi-stage model as the most reasonable, reflecting both the laboratory knowledge (Berenblum-Shubik, initiator-promotor) and the epidemiology (Armitage-Doll). It seems to be deficient in explaining at least two phenomena, however:

   a. Childhood cancers, particularly childhood leukemias

   b. Declines after an initial increase in (absolute) incidences of some forms of cancer (following some industrial exposures), including some lymphomas.

   An exhaustion of a "sensitive" population may have to be invoked for the latter phenomenon. I have some concern about "virulence" of cancer as possibly related to dose or exposure. I know of no data on this.

2. NOEL-ADI (Dourson - presentation).
   a. This is an interesting idea, worth follow up and further development. Two things, in general, are missing:

      i. Use of dose-response relationships
      ii. Use of information about sample size (Charles Brown of NCI has shown that for small sample sizes the highest dose (d_3) in one experiment in which the true responses were: d_1=.01, d_2 = .05, d_3 = .10, also had the highest probability of being selected as the NOEL. It was not until the sample size was in the vicinity of n=80 for each dose and controls, that the probability that the NOEL lay below d_1, was greater than 0.5.)

   As long as NOEL's are defined in terms of "statistically or biologically significant" increases issues of sample size will be important. (Does an objective, agreed-upon definition of "biologically significant" exist?)

   b. The "bench-mark" approach suffers some of the defects one has in cancer-modelling, i.e.

i. Choice of bench mark level, e.g., .1, .01, .001

ii. Dose-response model for extrapolation downward - what model? If a model with a threshold, how is threshold arrived at? If a threshold, hasn't one then arbitrarily defined the NOEL? If no threshold, then, no NEL, even if one could argue that there was an experimental NOEL.

3. Cancer-modelling - early stage, late stage effects (Crump)

a. This is a very useful extention of the Day-Brown, Whittemore-Keller work based on Armitage-Doll. I have a few general comments, and a few specific comments.

i. The animal studies conducted to date seem incapable of describing more than 2 stages, initiation and promotion. (Although I have seen one study which describes two stages within "promotion.") I would recommend some joint work between EPA and NTP to design animal models capable of distinguishing more stages - and at what stage(s) the carcinogen is operating. It must be recognized, in addition, that the animals used are usually genetically more homogeneous than humans and may, as a consequence show fewer (apparent) stages than would humans.

ii. I would like to see Tables 1 and 2 (and related tables) redone to show the effects of a "remaining lifetime" exposure resulting from modifying a dose - rather than showing a fixed numbers of years effect. For example I would like to see a table giving effects of exposures d from age 0 to ages 20, 40, 60, then followed for the remaining lifetime (use U.S. life tables - say it would be 55 yrs, 37 yrs, 21 yrs - or something like that) to a dose d/10, d/100. This would mimic the situation that EPA is faced with in reducing exposures from d to some d/q - which, it is assumed will then not be exceeded for a remainder of a life-time. Some other, probably more realistic life-time exposure patterns could be decided upon- and the table constructed for these. OSHA (or NIOSH) should have some interest in this, too, as shows CPSC. (Question: Does N. Breslow's paper in Jour. Am. Stat. Assn., March 1983, have any bearing on this problem?)

iii. I would like to see some parallel tables for materials which appear to act at more than one stage - e.g., cigarette smoke, and, if we keep all forms of cancer together, asbestos. Some animal data might be useful here, too- e.g., 2-AAF in the ".01 study" - with both bladder cancer and liver cancers.

iv. Heuristically, an association between early stage, late stage and initiator-promoter, and "shown mutagenic", "not shown mutagenic" can perhaps be made. I would suggest collaboration work between Dr. Crump and some EPA/NTP/NCI biologists to work out the appropriate ways to say this.

v. Some details:

(1) The two parts of the Tables 1 and 2, labelled "same total doses" and "same dose rate" are only expressions of different cumulative dose. In Table 1, the "same dose rate" piece reflects half the total dose of the "same total dose" piece (i.e., 35/70). In Table 2, the relative dose is 2/7 (i.e., 20/70 = .2857).

(2) I do not understand (in conceptual terms) the apparently opposite direction of certain effects - e.g., Table 1:

First stage only Age beginning	STAGE				
	3	4	5	6	Note
0	1.75	1.88	1.94	1.97	Upward trend by stage
20	0.71	0.52	0.37	0.26	Downward trend by stage
Penultimate stage only					
0	1.0	0.62	0.38	0.22	Downward by stage
20	1.37	1.44	1.36	1.22	Up and down
35	1.0	1.38	1.62	1.78	Up by stage

Is there some way to make (or help) a person understand how/why these different directions in trend are reasonable?

vi. The determination of the number of stages and which stages are affected seems to very critical. Is there some objective way to do this? (See my earlier suggestion re: animal experiments) there seems to be a related problem in the animal experiment (EDB) analyzed by Crump. There a distinction needed to be made in tumors causing death and tumors discovered at time of death as an incidental, non-fatal event. (see Crump p.13)

Finally if one postulates some number of stages and argues that the carcinogen operates at only one of the stages, is there any (intellectual) necessity for explaining what produces effects at the other stages- i.e., what makes the other stages come about?

vii. Comment on Table 4:

The hundred-fold differences between the week 49 stage 1 dose (4.7 mg/kg?) and the week 105 stage dose (0.048) is of considerable consequence when looking at possible human experience - where about half of all cancer deaths occur in persons older than 65.

viii. Page 19 of Crump.

The speculation on the reasons for non-linearity is very important, implying that pharmacokinetics needs to be investigated rather thoroughly. A lot of work needs to be done on this possible reconciliation. Because of the peculiarities in trend (Tables 1 and 2) with stage, e.g. if stage is not the source of non-linearity, then very different "safe" doses are likely to be recommended.

SESSION I-C

Some comments included above under "bench mark" considerations. My general impression is that using graded, or continuous responses (which, in effect, uses more of the data than does using quantal responses) will lower NOEL's.

SESSION I-D

Some comments included above under Session IA. No further comments - other than indicating relationship to Crump speculation on non-linearity.

SESSION I-E

Little new material was presented. See my comments on additivity of EXPOSURE/ADI ratios for similar effect. For cancers, either confine this summation to cancers at the same site - or, with somewhat more sophistication- to cancer arising out of tissues of similar embryonic origin - perhaps all carcinomas, all blood-forming tissues (plus lymphomas?), all sarcomas. Advice from pathologists should be sought. John Berg (Iowa) has done some work along these lines while considering multiple primaries.

SESSION II-A Structure-activity relationships

This is an area of promise, and needs to be supported. The only other claimed to a useful SAR approach that I know of is the electrophile approach by the Millers of Wisconsin. Enslein's results should be compared with the Millers' - and the reasons for disagreement (I am sure there are disagreements) worked out- if possible. I would like to see a detailed exposition of the Enslein process including:

1. The discriminant equations
   i.e., what parameters contribute most to separating materials later labelled as carcinogens from those labelled non-carcinogens? Are these parameters different for different classes of chemicals? If so, how are classes of chemicals defined, or determined in advance?

2. What kind of self-learning process is built into the Enslein procedure? How have the parameters changed with additional data? How are missing data handled?

3. Comparisions of Enslein equations with other SAR approaches- and with such testing procedures as short-term mutagenesis tests. This would (or should) include a proposal for step-wise testing (evaluation) of potential carcinogens. Can the Enslein process be set up with cut-off points that we can be sure will not be carcinogens? If this could be done, a great deal of testing might be eliminated. Some cooperation with NTP seems in order here.

   Numerical comment. I believe there is a theorum in discriminant analyses that says the discriminating power of any discriminant equations must be lower for every set of data in comparison to the data set from which the equation was constructed. (A corollary to this is that the discriminant equation will change, i.e., will show the effect of "learning," as more materials are examined.)

   Concerning the question of why a black box (a discriminant equation) works, it is worth noting that the black box is not created from random elements, but rather that the parameters of the discriminant equations are chosen because someone thinks they have something to do with the outcome. Frequently much of the explanatory information is extraneous, and contribute nothing (additional) to the correct sorting-out process.

   Final question: Is there some way of adding the electophile information to the existing Enslein equations? If done, does it improve the discrimination?

SESSION II-B Reproductive effects

This area needs to be broadened to evaluate other effects if it is to be useful for assisting in the regulatory process. Specifically there needs to be consideration of pregnancy wastage, (spontaneous abortions), reduced fertility, etc.- as well as teratologic effect, malformations, etc. This impresses me as a nascent field, still in the descriptive or quantal phase. It is nonetheless useful.

To me these developments are possible:

1. Establishment of a minimum body of end-points to be looked for in these studies
2. Creation of data bases on spontaneous abortions (in humans) - and subsequent interaction between the epidemiologic and laboratory studies- including cooperation on "behavioral" toxicology.
3. Studies on effects on the germ cells in whole, intact, mammals.

SESSION II-C Mathematical models

Much of the discussion under IB, IC is related. Response models as well as dose models need to be considered. I see needs for considering:

1. Effects of peak doses versus effect of cumulative doses (there are pharmacokinetics issues here)
2. Population variability- e.g., the population distributions of t, in the equation (by Hertzberg)

   $D_1 < (t_1A(t_1)-D_0t_0)/(t_1-t_0)$ $t_0 \leq t_1 \leq l$
   where l=lifetime

3. Tissues-specificity problems - both arising out of first-pass considerations and other mechanisms

WORKSHOPS:

A-1 Considering high risk (sensitive) subgroups in health risk assessment.
(What follows is the report of this workshops.) The group came to these (agreed-upon) conclusions.

1. One "safety-factor" number (i.e., division by 10 or 100) is inadequate to take into account the variability in the human population. Safety factors developed for adults are inappropriate for use with children.

Action: Develop more data relating to safety-factors for different segments of the population. In the interim to use current factors, setting a deadline for when they should be reconsidered.

2. For future changes in safety factors, base safety factor on (more) data on:

   a) Slope of the dose-reponse curves (The shallower the slope the larger the factor needs to be)

   b) The specific toxicity and its severity (the greater the need to protect against the toxicity, the large the safety factor needs to be. A life-time of illness or reduced functional ability is usually more important than a short-term, reversible, incident).

3. For non-cancer effects, remain with the ADI concept, rather than a "hazard index". While the public-health consequences are greater when more people become ill (hazard index), it is individuals who become ill, and even a small number of persons are to be protected against serious consequences.

By way of back up of these agreed-upon conclusions the participants considered these questions (stimulated by Erdreich presentation):

1. What contributes to sensitivity in addition to demographic factors?

   a. Prior exposures to same, and other materials
      Genetic background
      Existing other illnesses
      Special dietary sub-groups

Data are largely confined to drugs and rarely exist for non-intented effects, although some interaction data with common human activities (i.e., exposure to alcohol, cigarette smoking) do exist.

Some data exist on humans- measured, controlled, consistent among individuals.

2. What resources exist to desribe the variability?
   (Data bases or follow-up groups)

   A. Registries of special diseases or conditions, e.g., bronchitics, persons with transplants, cancer registries:

      Framingham
      Michigan
      Fels Research Institute data- for follow-up of some children's groups

Special exposure groups
  -industrial
  -Love Caval
HANES
NIH-NICHHD- peri-natal follow-up group
Retirement (e.g., Leisure World) populations etc.

3. Should chemical-specific lists of high-risk groups be established?

   A. Yes, and the lists should be cross-indexed by effect, and sensitive group as well as by material.
   e.g., Phenylketonurics (aspartame)
   Asthmatics
   Persons with angina
   Alcoholics etc.

4. Is pharmacokinetic information (existing data) partially useful in this area?

   A. Yes, but recognize shortcomings- not a direct measure of health effect, e.g., more rapid or intense response in "sensitive" persons. Factors related to receptors- likely to be genetic, but nonetheless chemical-specific (One must not assume uniformity in a population with respect to behavior of receptors)

The participants also reviewed some issues varied by Hattis. He outlined these contributions to variability:

I. Non-chemical specific: cross-sectional studies of humans likely to provide some useful data.

   a. Things causing variability in exposures (often route specific):

      Body size - see children - greater water intake per unit weight or surface

   b. Overt disease states- pushing persons closer to a thresholds
      Angina
      Asthma
      Nerve-conduction defects (increasing reaction time)

   c. Physical inhibition (or excitation) of function by prior exposure:
      Alcohol (liver function)
      Smoking (hemoglobin availability).

II. More likely chemical specific- requiring studies of individuals
Pharmacokinetic
Parmacodynamic

[End of this workshop report]

Workshop A-2

I see three serious issues:

1. The rating values for toxic effects have fuzzy boundaries
   - reversibility seems not considered
   - germ plasm effects?
   - life-time effects (e.g., reduction in functional ability, reduced IQ)

2. Dose producing effect
   - perhaps, rather than in absolute units, may be reported as a proportion of the anticipated dose to humans

3. Scoring system implies a logarithmic scale (equally spaced in the log) for both effect and dose. This needs a lot of justification. The boundries for RQ's are arbitary. Some justification must be made.

This process is far from ready to be used for extrapolation to NOELs. At this stage of development, I can see a lot of controversy, and only a little gain.

SUMMARY SUGGESTIONS FOR FUTURE MEETINGS

I found the two workshop sessions I attended as the most useful expenditures of time. This leads me to suggest:

1. Keep future meetings small

2. Have workshop sessions on first day - from which a written report is made to the whole group - and is made available by the next day
3. Have a pre-set format for the report, and a set of questions for the workshop to answer. Assign a specific (contractor?) person to assist the rapporteur in preparing each workshop report, so that the reports might be complete. I think each report might be required to address the following:

   A. Action recommendation - what to do now, and up to such time as further data become available

   B. Appropriate additional research to answer

   C. Unresolved issues of substantial consequence.

4. Have the whole (small) group meet on the second day to consider the workshop reports, to make necessary changes, etc. - leading to

5. A final report to EPA with recommendations (in the same format as the workshop reports) to which the whole group will agree- or to which some members will prepare minority reports.

ENVIRONMENTAL DEFENSE FUND

MEMORANDUM

TO: C. Cueto, PhD
FROM: E.K. SILBERGELD, PhD EKS (b1)
RE: Risk Assessment Meeting
DATE: 18 July 1983

This constitutes my postmeeting memorandum, and follows the outline as indicated in your memorandum of 11 July.

As a new participant in this ongoing discussion of risk assessment, I would have found it very useful to have received more premeeting briefing material on the past sessions of this group and on the progress of its earlier consensus. It took about half of the first day for me to understand the structure and process of this group. When I did, I came to appreciate the method highly, but it is a difficult one to jump into without prior knowledge.

As a second general comment on this workshop, I would like to express my overall concern (which will be detailed below) that we failed to deal with noncarcinogenic toxicants, despite the topic headings. There are significant differences in carcinogenesis, as compared to other types of toxicology, in the types of data available as well as the appropriate models which can be used to extrapolate from datapoints in order to estimate effects at lower doeses. This discussion group needs to focus more specifically on noncarcinogenesis toxicology.

CONSENSUS TOPICS

I. Interspecies conversion of dose and duration of exposure

ECAO wants an approach which provides the most appropriate and inclusive use of data derived from a range of experimental animals in order to estimate risk to humans. There are

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problems related to differences in body size and in relative lifetimes. I was not present for this discussion during the general presentation on day one; however, I gather that consensus was generally reached on the use of a dose/body surface area or cube root of weight approach, since those method give some accomodation to organ:body weight ratios and have some relationship to metabolic rate (e.g., liver:body surface area).

My concern with this approach is that it is relatively easy to think of examples which confound any generic approach--e.g., the qualitative differences in caffeine metabolism between humans and rodents. However, there is obviously a need to develop generic approaches, particularly when data are not available. My own research in pediatric pharmacology has been based on surface area adjustments, so this approach has some clinical justification.

II. Risk assessment for less than lifetime exposure (toxicants)

The consensus appears to have adopted the usual pharmacological conventions of 0 -5 days as acute exposure; 5 -14 days as subchronic; and 90 days as chronic.

I did not hear a discussion of comparing physiologically similar life stages: e.g., the first 6 days of rat gestation with the first trimester of human pregnancy, or the rat's first 20 days of postnatal life with the nursing period of infants.

III. ADIs based on quantal, continuous or graded data

This session proposed a rather fundamental revision in the way in which health risk assessments are to be done. Although the title of the session was directed towards noncarcinogenic toxicants, most of the presentation by Crump, and the subsequent discussion, was focussed on carcinogens. The proposal by Crump was that instead of applying models (such as Mantell-Bryan; Weibull, Armitage-Doll, etc.) in order to draw dose-response relationships beyond the range of the data, EPA should only use dose-response data within the range of actual experimentation (or epidemiological observation). Also, instead of working to establish NOAEL points through experimentation, research should concentrate upon the definition of "benchmark" (or, in Nelson's term, pseudo-NOAEL, although I think this is a misinterpretation of Crump's proposal), and then apply appropriate safety factors or other divisors in order to define an acceptable level.

I do not think that consensus was reached on this topic. For one thing, Crump's paper was not easy and was not discussed in depth at the meeting. For another discussion (such as it was) focussed only on these hypotheses as applied to carcinogens. Crump did not have time to discuss his models for noncarcinogenic toxicants.

More importantly, I have grave reservations about this approach. I fear that it really begs the question. While I endorse the concept of working from defined effects, rather than nebulous and often highly debatable NOAEL doses, I think that the way in which one would "work down" from such benchmarks would be highly dependent upon the type of toxic effect observed. For a neurotoxicant, for example manganese, this benchmark might be 50% inhibition of tyrosine hydroxylase in the basal ganglia. Considering the great importance of this enzyme in central control of neuromotor function, one might apply a rather stringent divisor to the dose and consider that a ten-fold less exposure is the highest ADI. But in the case of a hepatotoxin (succinyl acetone), where the benchmark might be 50% inhibition of the enzyme ALA dehydrase, knowledge of the greater functional reserve of this system might permit a less stringent division of the benchmark dose to estimate an ADI. Thus, I am not certain that this approach really advances us very much.

In the case of carcinogens, this approach would constitute a significant change from the current methods of CAG. It should be very carefully reviewed, and some estimation of its impact, in a regulatory sense, should be undertaken by ECAO. Some of us have had experience of similar revisionism in Dr. Albert's 1981 proposals for carcinogens, which would have raised the "ADI" for dioxin by about 2,000 times.

IV. Route-to-route conversion

EPA is interested in using data obtained from experiments using one particular route of exposure in estimating health effects of exposure through another route. This has clear utility and would reduce the amount of experimentation needed before regulation an airborne carcinogen, for instance, after a water criteria document has been researched and published. It was proposed that such route-to-route extrapolations could be acceptable under certain conditions: when the portal of entry (lung; GI tract; skin) is not the target or critical organ; when firstpass metabolism is not of major importance; and when conditions of exposure (coupled with metabolism or activation) are not such as to produce rapid changes in plasma levels in intermittent exposures. Both Doctors Withey and O'Flaherty presented interesting datasets indicating the pitfalls presented by cases which violate these preconditions.

Consensus was genrally reached on this approach, although some reservations were expressed on specific chemcials.

V. Multiple chemical assessment

EPA requires some method of integrating the combined risks of exposure to multiple chemicals. A model was presented by Hertzberg and Durkin related to dose additivity. There was a lack of acceptance of this approach, particularly in its fractional approach (i.e, those affected by the first exposure would not be affected by the second, etc.). The model does not appear relevant to the major questions related to multiple chemical assessment: interaction of toxicants; synergism/antagonism of specific agents; likelihood of coexisting health effects in one individual (i.e., tumor, hepatotoxicity, nerve damage, immune dysfunction can all occur in one animal exposed to dioxin; hepatotoxicity, CNS and peripheral neuropathy, and hematoxicity can all occur in one individual exposed to lead). I did not find this an approach which was likely to be useful to ECAO.

In cases where one highly toxic substance can be identified in a mixture (i.e., dioxin), EPA may be better by basing assessment on that substance alone. In cases where substances are identified and are known to affect different organs, then each effect must be assessed and the overall result considered within the framework of effects ranking (see discussion of workshop topics below). In cases of unknowns, there is very little to choose from in order to guide assessment. Dose additivity is clearly insufficient, yet total separation of each substance is not appropriate. This subject requires much further discussion.

NEW TOPICS

I. Structure-activity analysis

Two presentations were made on the use of chemical structure in modelling an predicting toxicity. I found this discussion baffling. It was admittedly unrelated to what is usually considered the basis of structure-activity analysis--that is the use of mechanistic hypotheses to generate "families" of similarly acting agents. The methods described by Broderius and Enslein appear to be solely empirical in that lists of reactive chemicals are entered into the model and equations derived from these lists. These lists work well on an internal basis--that is, they predict the behavior of those chemicals used to develop them. That is not terribly impressive. As Broderius indicated, his models for bioaccumulation and fish toxicity work best in describing compounds of relatively low toxicity. The need for SAR is to warn us of the highly toxic substances, not to rank low-concern chemcals. Comment was made that "true" SAR of the type done by Kaufman at Hopkins is very expensive. However, its success has great implications for highly accurate and valuable predictive strategies. ECAO would do well to support this type of SAR, rather than the type presented at this meeting.

II. Reproductive toxicity

ECAO is concerned to develop methods of assessing risk of reproductive effects of chemicals. This is an area of tremendous public concern, and the Agency should overcome its failure to propose standard methods of reproductive toxicity testing under TSCA, as well as its lack of research on reproductive effects in dumpsite studies.

Manson gave an elegant presentation on two types of teratogens; a direct acting teratogen whose activity can be predicted because of its special toxicity for cells in mitosis, and an indirect teratogen whose less predictable effects appear to be related to hormonal modulation of organ development. The presentation indicated the need to develop wide-ranging and sensitive indicators of adverse reproductive outcome. However, by its focus, this discussion did not cover nonteratogic reproductive toxins. I mentioned two other types likely to be of great importance in ECAO's assessments: fetotoxins, substances to which the fetus is more sensitive at lower dose than adult organisms; and gonadal toxins, substances which affect the sex organs, their physiological function, and the germ cells. No consensus was reached on this topic, and must of the sense of the meeting was concern over the apparent complexity of this area of toxicology. Further discussion is greatly required, particularly since this field will be important in dealing with issues of severity of effects and specially sensitive subpopulations (see below).

III. Mathematical models

This presentation was also less than appropriate to the complexity of real-world toxicological data. The model's structure was highly linearized, and omitted any Michaelis-Menten type kinetics which are highly relevant. It is suggested that ECAO consider the model for procarcinogens recently published by Hoel in Science as a more reasonable approach to this type of modelling. In this topic as in others, I am concerned about the lack of appreciation by ECAO of the mechanisms and dose-response relationships for noncarcinogenic toxicants.

WORKSHOP TOPICS

I. Hypersusceptible subgroups

As indicated by Bingham, EPA is reconsidering its generic approach to covering variations in human susceptibility by one overall factor of 10. There was general consensus that this range is likely to be insufficient to cover fully the range of responses of major subgroups in the population, such as children. Nisbet pointed out that children are at increased risk by their greater rate of uptake (inhalation, ingestion); their behavioral interactions with the environment; their propensity to remain outdoors; their underdeveloped metabolism; and their increased sensitivity of some critical target organs (such as the brain). It was suggested that increasing the factor might account for this, but as I pointed out, in some instances different groups may actually present with a different critical organ for toxic effect--e.g., the work of Manson demonstrating the highly specific sensitivity of the fetal heart for disturbances in T4/T3 metabolism.

Erdreich presented a good discussion of the data in pharmacogenetics and proposed that analysis of this data might be relevant for estimating the types of variance in response (e.g., log-normal or multi-modal). This was endorsed, and additional sources of data were also suggested (such as the Fels Institute longitudinal studies).

The paper of Hattis, restricted as it was to acute effects, was not particularly helpful. Moreover, it was not accepted that population variability should be incorporated into a hazard index; the consensus of opinion was that this should be factored into setting the ADI, which is then used in determining hazard indices and other assessment variables.

II. Use of exposure data in assessing health risk

This workshop group focussed its discussion on a perceived discontinuity between environmental monitoring/modelling and epidemiology (or the monitoring/modelling of population factors which determine exposure). The group agreed that this lack of communication, which affects both scientific disciplines and the various offices of EPA, needs correction. Increased data are generally needed, particularly in monitoring, and there should be opportunity for feedback on second tier studies. Further consideration of this topic should include epidemiologists, particularly those who have studied exposure as well as disease associated with that exposure.

On the other workshop topics, which I did not attend, I have particular concerns about the ranking of severity of effects. The table included in the premeeting materials was not apparently much discussed. It is greatly biassed towards pathological findings with hyperplasias and necrosis in all cases ranked more severe than biochemical changes. Some statements are so unqualified as to be uninterpretable--e.g., what does "any decrease in reproductive capacity" include? The difference between "death" and "pronounced life-shortening" is not clear--how is life shortened except by death? Why is teratogenicity without signs of maternal toxicity more serious that teratogenicity with signs of maternal toxicity? It may be the case that maternal effects are quite different (and possibly less severe) from fetal effects. Some appreciation of reversibility/ir- reversibility should be incorporated into this table; also, possibly some organ-specific considerations--that is, it is probably always worse to damage ova rather than sperm, since sperm are replaceable while ova are fixed in number during prenatal developments.

OTHER COMMENTS

I would suggest consideration of the Monitoring and Assessment Research Centre publications by ECAO in its further work on these subjects. Moreover, more presentations of that they show real toxicology data in some detail, so that we can better understand the utility of some of the models to these data. For some other approaches to SAR, I suggest inviting Joyce Kaufman or David Rodbard (NIH) to discuss real SAR approaches, using computer models of agent-receptor interactions.

For another approach to interactions of toxicants, you should consider the new work by Klug's group on carcinogenic metals which act at catalytic sites in DNA (a new contribution to the threshhold/nonthreshhold debate). Also, I enclose a statement by the Dahlem Conference workgroup on mechanisms of metal toxicity, which you may find useful. You could invite Dr. Robert Willimas of Oxford to discuss his model approaches to toxicity of metals.

OTHER TOPICS FOR DISCUSSION

1. Environmental epidemiology.
2. Quantal vs. continuous effects of toxins.
3. Neurotoxicity.
4. Models of metabolic activation (Hoel).
5. Studies on waste streams as examples of multiple chemical mixtures (see NY State Department of Health studies on "Binghamton soot," attached).
6. Bioavailability.

Health and Welfare Canada
Santé et Bien-être social Canada

Health Protection Branch
Direction générale de la protection de la santé

Sir Frederick G. Banting
Research Centre,
Tunney's Pasture,
Ottawa, Ontario
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July 20, 1983

Your file Votre référence

Our file Notre référence

Dr. C. Cueto,
Project Director,
Dynamac Corporation,
The Dynamac Building,
11140 Rockville Pike,
Rockville, Maryland
U.S.A. 20852

Dear Dr. Cueto:

Attached are my post-meeting comments for the recent methodology meeting held in Cincinnati July 12 and 13th last. I thought that the meeting was, on the whole, fruitfull in crystallizing some of our thoughts on important areas. In others, we were less than definative.

If I were to be asked for suggestions on the "next step" I would recommend that we apply some of our approaches to real situations. There is probably enough data in the literature, for example, to apply some route-to-route extrapolation procedures, to assess ADI's for complex mixtures (dump site monitoring data) and to do some calculations on multiple route effects.

Above all, I must strongly recommend that the presentations and some of the discussion following, be published in a form which can be referenced and cited. It would be a pity to go over old ground repeatedly.

I very much enjoyed meeting with you and your staff. I trust that all of my documentation, including copies of my presentations and slide material, was in order. If you require additional help with this please ask.

Sincerely,

Jim Withey

Jim R. Withey
Toxicology Research Division,
Bureau of Chemical Safety.

JRW/mad

Attach.

POST MEETING COMMENTS

Methodology Meeting, U.S. Environmental Protection Agency,
Cincinnati, Ohio, July 12-13th, 1983

1. Route to Route Extrapolation

(i) It would appear that our thoughts on the pharmacokinetic approach have been consolidated to a point where, given the values of rate coefficients, absorption coefficients and the exposure regimen, extrapolation from inhalation to oral uptake, and the temporal relationships for systemic levels, could be constructed. We agreed that, in the case of the oral route, first pass effects are an important aspect of the assessment but does not necessarily exclude the application of quantitative route extrapolation procedures.

Some special mechanisms, such as the deposition of aerosol and particulate matter in the lung followed by uptake to the systemic circulation; need to be considered as a factor which may preclude route extrapolation.

(ii) The Stokinger-Woodward approach is crude and should be avoided wherever possible. The S-W method, where ~~gavel~~ good absorption coefficients for both the oral and inhalation routes are available, will correctly predict the relative amounts which are taken up into the systemic circulation. As my case 3 shows, relative rates of uptake and elimination may be unimportant in determining the temporal relationship for systemic levels. In such cases, the S-W method will be as good as any sophisticated pharmacokinetic methodology.

(iii) It would be interesting to have a list of those compounds, which are in the AWQC list, for which the S-W approach was used.

.../2

(iv) I should like to have an exposure scenario which might be considered more realistic than the one I used to illustrate the blood level-time curves in my cases 1, 2 and 3. You will recall that I used a 10 hr. vapour phase exposure and either 4 or 20 oral doses over a 10 hr. period. Perhaps a 24 hr. inhalation exposure period might be more applicable. It would also help if different pharmacokinetic models (ie. a 2 or 3 compartment) and specific rates of uptake, distribution and elimination (the hybrid rate coefficients) were used. Any feedback on this which would represent a more realistic appraisal than those used, for illustrative purposes, in my examples will allow me to feed my computer and generate some interesting figures.

2. Species Extrapolation

We were treated to a good presentation and some lively discussion on the biological rationale for dose as assessed on an animal body weight or body surface area or some power law of each of these. These relationships are, however, empirical.

As I mentioned in the discussion, a much more rational approach has been suggested by Dr. Jim Gillette in several publications (Gillette, 1976; Gillette, 1977). I enclose a hard copy of both of these for your interest. While we may not have all of the information required for this kind of conversion it should be used as a beacon for further consideration.

I am particularly concerned about species with metabolic deficiencies. I have reviewed this subject recently and can give you some examples:

(i) Wide species differences in enzyme activity eg. a 50-fold range for the metabolism of hexobarbital (Quinn et al., 1958).

.../3

(ii) Different conjugative pathways for phenols. The pig and the rat excrete the glucuronide and sulfate; sheep excrete phenols as the phosphate (Kao et al., 1979).

(iii) Rats can not N-hydroxylate aliphatic amines, guinea pigs can not N-hydroxylate aromatic amides nor produce mercapturic acids. (Caldwell, 1981).

(iv) Cats do not produce the glucuronide of phenols or aromatic acids and dogs find it difficult to acetylate primary amino groups or to effect some kinds of acyclic hydroxylation (Caldwell, 1981).

(v) Small rodents tend to use glutathione for detoxification rather than water and the ratio of glutathione transferase to epoxide hydrase activities is much higher in the rat and mouse than in non-human primates and man. Thus the rat and mouse use valuable protective materials as their first line of defence whereas man and primates use glutathione only as a reserve after water and epoxide hydrase have exercised the primary protective effect (Pacifici et al., 1981).

(vi) A comparison of species as adequate metabolic models for man is summarized in a review on this subject (Smith and Caldwell, 1976).

3. Multiple Exposures

I was a little concerned that the sum of intrinsic activities for a series of compounds in a mixture was accepted so readily. As I pointed out in a recent appraisal (Withey, 1982) interactions can affect, quite considerably, all aspects of pharmacokinetics. In particular, if I was asked to assess the human health impact of a dump site which contained polycyclic hydrocarbons, or other inducers of the mixed function oxidases, I should want

.../4

to accept much lower estimates for the acceptable exposure to aromatic halogen compounds, like the PCB's, and other hepatotoxic and carcinogenic compounds.

4. Exposure Data

I have little to say on this difficult issue. Clearly, the discussion established that models, particularly for air, are difficult to construct. It would seem to me that the figure 1. Information Flow and Methodology Use in Conducting Site-Specific Multichemical Risk Assessment, Showing Use of Each Methodology Component Under Development by ECAO-Cincinnati can now be reconstructed with a much larger "box" for Exposure Assessment. Someone must address this topic and set the GOAL and type of METHODOLOGY USED. It would also seem that there is a need to reorganize this diagram to illustrate cross interaction at various stages. In conclusion, I think that the methodology discussions have been hampered by a lack of site-specific information.

J.R. Withey,

July 20, 1983

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EPRI
Electric Power
Research Institute

September 7, 1983

Dr. Jerry F. Stara
Director, Environmental Criteria
and Assessment Office
U. S. Environmental Protection Agency
26 West Saint Clair Street
Cincinnati, OH 45268

Dear Jerry:

I am sorry to be late with my post-meeting memo.

Consensus Topic: A. Interspecies Conversion

The current approach is based on surface area differences.

The consensus appeared to be a request for greater flexibility. In the presence of uncertainty, the most conservative approach (based on surface area ratios) should be followed. There are cases, however, where alternative methods (e.g. ratios of body weight) may be more suitable; in such cases, they should be utilized.

I would personally urge that more use be made of pharmacokinetic models where they can be demonstrated to fit the available data.

Consensus Topic: B. Less than Lifetime Exposure

Although both options were clearly presented, there was no clear consensus here with respect to toxicants. I believe several more examples would help clarify the differences between the two options as well as indicate which performs most consistently. Option 2 should consider alternative dose-response curves to the log-log as well as consider weighted curve-fitting procedures; which take into account the quality and quantity of data used to derive the curve.

For carcinogens, there was a general consensus in favor of option 3, although some modifications were suggested. The Crump-Howe method could be simplified by applying it to some prototype population distributions, and some allowance should be made for those cases where the multi-stage model does not appear to fit the data.

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Consensus Topic: C. ADI's Based on Quantal, Continuous or Graded Data

There seemed to be greater support for second option than for the first although there still seemed to be some holdouts in favor of the present NOAEL-safety factor approach.

Consensus Topic: D. Route-to-Route Conversion

There was general consensus that a flexible approach was the best one. Lack of suitable data and the inconsistent performance of existing models cannot lead to the recommendation that one approach be exclusively followed.

Consensus Topic: E. Multiple Chemical Assessment

There was greater support for the second option although a suggestion was made that the first be undertaken as well in an effort to bracket the true risk of multiple exposure. In any case all of the factors associated with multiple exposure should be identified.

Workshop Topic: A1. High Risk Subgroup

There was consensus that special attention need be given high risk subgroups and that the safety factor of 10 utilized for population variability may not be sufficient to protect all high risk subgroups. No consensus was reached, however, about how to resolve the high risk subgroup problem.

Workshop Topic: B1. Multiple Route Exposure

This group developed detailed guidelines with general agreement about five conditions for summing exposures across all routes.

1) dose-duration patterns should be identical across routes.

2) System effects should be identical across routes.

3) there are no effects at portal of entry.

4) there are no first pass effects.

5) D/R/T known for at least one route in terms of internal dose.

With lesser information, extrapolation estimates become more tentative.

Workshop Topic: A2. Ranking Severity of Effects

There was support for the concept of ranking by severity of effect but there was no agreement about the approach taken to achieve the goal. More illustrative examples of alternative approaches may serve to clarify them and lead to more definitive conclusions.

Workshop Topic: B2. Exposure Data

There was a consensus statement prepared about exposure assessment. I believe, however, more detailed presentations by Jim Falco of the EPA Exposure Assessment groups could lead to even greater consensus about this topic.

New Topics: A. Approaches Using Structure-Activity Relationships

It would be useful to learn about additional approaches for these models to compare the performance of alternative techniques. I'm hesitant to use these approaches when other (e.g., toxicologic or health) data are available however, in the absence of any information these relationships appear to be the only tool available.

B. Reproductive Effects

My interpretation of Jeanne Manson's talk was that these effects are relatively rare and major attention should not be given to these effects. I found Dr. Manson's presentation to be clear, coherent, and convincing but the conclusion was contrary to my lay predisposition. For that reason it might be useful to invite other well-known teratologists to address the group at future meetings to ensure that there is a reasonable consensus about these effects. Perhaps someone familiar with the existing and developing clinical data bases in this area could be of help (i.e. James Hanson, University of Iowa or a representative from CDC).

C. Use and Biological Justification of Mathematical Models

Dr. O'Flaherty's presentation was clear and reinforced the importance that should be addressed to first-pass metabolism. Some provision for this effect should be incorporated into our work.

I hope these comments are helpful, if you would like any further discussion of any of them, please feel free to telephone me at (415) 855-2577.

Sincerely,

Ronald E. Wyzga, Sc.D.
Technical Manager
Environmental Risk Analysis

REW/cdl

cc: Cipriano Cueto

SECTION 3

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SECTION 4

BACKGROUND REFERENCES

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Proceedings, October 1981

New Orleans, Louisiana
December 10–11, 1980

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Section 3

WATER QUALITY CRITERIA: METHODOLOGY AND APPLICATIONS

J. F. Stara et al.*

INTRODUCTION

In the last 20 years there has been an almost overwhelming proliferation of chemicals in our environment. In 1977, for example, there were more than 60,000 commercially significant chemicals, and additional compounds were marketed at the rate of 500 to 700 per year (1). These figures do not reflect the staggering diversity of compounds developed but not produced in commercially significant quantities. They do illustrate that water basins in the United States are being polluted by increasingly complex municipal and industrial discharges (Figure 1). This contamination by point-source pollution is predominant in the water basins of Northeast, Great Lakes, North Central Regions, and Islands (Table 1).

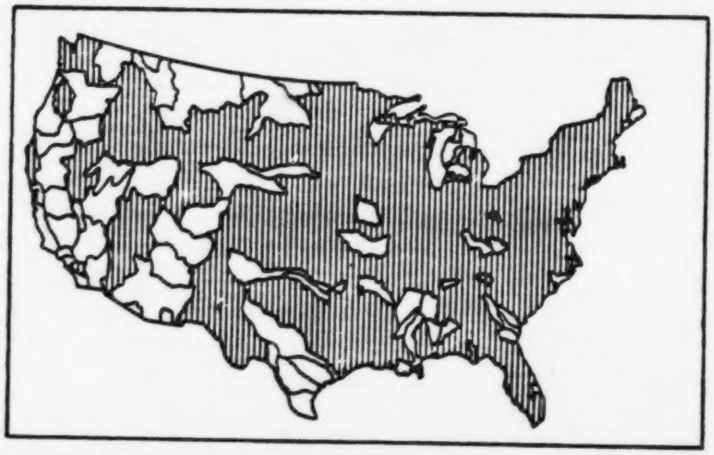

Figure 1. Basins affected (in whole or in part) by industrial discharges, 1977. Shaded areas show basin areas contaminated by industrial discharge. (Source: US EPA, *National Water Quality Inventory: 1977 Report to Congress*, 1978)

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* M. L. Dourson and C. T. DeRosa; Office of Environmental Criteria and Assessment, US EPA, Cincinnati, OH.

Table 1

POINT SOURCE POLLUTION BY REGION, 1977*

Region	Number of Basins	Percentage Affected by Type of Source**		
		Industrial	Municipal	Combined Sewer Overflow
Northeast	40	95	95	60
Southeast	47	74	91	17
Great Lakes	41	80	95	37
North Central	35	74	86	6
South Central	30	70	100	0
Southwest	22	23	64	0
Northwest	22	55	73	14
Islands	9	89	100	0
Total	246	72	89	20

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*Source: Reference 2

**In whole or in part.

The ubiquitous nature of such pollution poses a difficult dilemma for public health officials. A significant proportion of our population is being exposed to chemicals that have yet to be assessed with respect to their potential health hazard. From the standpoint of public health, possible biological effects include: acute, subacute, or chronic toxicity; mutagenicity; teratogenicity; and carcinogenicity. Clearly, in the absence of appropriate control technologies, the unrestrained chemical contamination of the environment represents a significant threat to public health.

HAZARD EVALUATION METHODOLOGY

The issue of hazard evaluation or assessment deals specifically with potential routes of exposure and associated health risks. Procedurally, such an assessment invokes the basic toxicological concept of dose-response relationships; in environmental terms, this translates as exposure versus risk. Although the Environmental Criteria and Assessment Office-Cincinnati (ECAO-Cin) has been most concerned with pollutant exposure through water, it is obvious that all routes of exposure should be considered in any assessment of hazard. For carcinogens, however, only incremental risks associated with contaminants in ambient water were considered.

A further distinction must be made between voluntary and involuntary risks associated with exposure. While society may routinely accommodate a defined risk level associated with a therapeutic drug for the treatment of a disease, it may reject any risk level associated with the presence of hazardous chemicals in drinking water. Occupational exposure falls somewhere in the middle of this continuum. Workers in the nuclear industry may, at times, accept a higher level of risk than the general population. On the other hand, the acceptance of enhanced risk levels is not entirely voluntary, and risks should be minimized whenever it is feasible to do so.

With the distinction between voluntary and involuntary hazards in mind, the precise nature of the risk associated with exposure to a particular chemical agent can be defined by using the biological endpoints discussed previously (e.g., toxicity, carcinogenicity, etc.). It is the consensus of scientists and the National Academy of Science (NAS) that these endpoints can be considered to be either threshold or nonthreshold phenomena (3). Biologically, threshold represents a no-effect level explained by an organism's resistance or sum total of defense mechanisms in the face of toxicological challenge. In contrast, chemical carcinogens are considered to be nonthreshold agents, since a single genotoxic molecule can be assumed to interact with the cell's DNA and, thereby, result in a malignant growth. While not all carcinogens are genotoxic, epigenetic carcinogens were treated conservatively using the nonthreshold hypothesis since sufficient scientific data are not yet available to resolve this issue.

The problems presented by chemical contamination of water resources are not unique to the United States. As a consequence, a growing number of countries have enacted legislation to regulate production, use, and release of chemicals (Table 2). The international flavor of the issue is further amplified by the fact that the World Health Organization (WHO) has proclaimed the 80's as the "Decade of Clean Water." Within the United States, the responsibility for regulatory measures and the development of guidelines is assigned to a number of agencies (Table 3).

The initial quandary to be confronted by such organizations and agencies is the bewildering ocean of chemicals that represent a potential hazard to human health. As a result, the first issue of concern is the relative priority of chemicals for hazard evaluation. Criteria for determining a specific chemical's priority for subsequent evaluation include:

- Extent of production and industrial waste;
- Use pattern;
- Persistence;
- Dispersion tendency;

Table 2

COUNTRIES AND ORGANIZATIONS THAT REGULATE CHEMICAL SUBSTANCES

Country	Legislation	Date
Canada	Environmental Contaminants Act	1974
France	Control of Chemical Products Act	1977
Federal Republic of Germany	Chemicals Act	Pending
Japan	Chemical Substances Control Act	1973
Sweden	Act on Products Hazardous to Man and the Environment	1973
Switzerland	Law of Trade in Toxic Substances	1969*
United States	Toxic Substances Control Act	1976
Denmark	Toxic Chemicals Act	Pending
European Communities	Directive for the Sixth Modification of the Council Directive of 27 June 1967 on the Approximation of the Laws of Member States Relating to the Classification, Packaging, and Labeling of Dangerous Substances.	1979

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*Effective 1972.

Table 3

UNITED STATES REGULATORY AGENCIES

Agency	Established	Authority
PHS	1798	Public Health Service Act of 1944
USDA	1852	Act of Congress
FDA	1907	Food and Drug Act
OSHA	1970	Occupational Safety and Health Act
EPA	1970	Executive Order: Clean Air Act Clean Water Act Toxic Substances Control Act
CPSA	1972	Consumer Product Safety Act
NIOSH	1973	National Institute of Occupational Safety and Health Established within PHS by Secretary of Health, Education, and Welfare.

- Biotic and abiotic transformation; and
- Human toxicity (most important).

Secondly, regulators must determine the best approach for the evaluation of human health hazard based upon a particular toxicological testing strategy. This often encompasses a third problem that relates not only to the extrapolation of animal data to man but also from short-term animal studies to lifetime exposure for human populations.

The final issue is cost. At present, an NCI bioassay can cost as much as $500,000; the required expenditure to test the 700 new chemicals of commercial significance produced each year would be $350 million. Even if government and industrial expenditures were properly integrated to minimize duplication of effort, the cost of an advisable testing protocol could not be met at current spending levels. As a result, the US population uses and is exposed to untested, or inadequately tested, chemicals of unknown toxic potential. Indirect cost considerations include the costs of regulation reflected by reduced industrial productivity and the costs to society in terms of human health in the absence of reasonable controls.

In promulgating controls and standards, government agencies have three distinct options. If sufficient evidence exists that a particular substance is a hazard to public health, it can be banned--as in the case of kepone. Alternatively, the use of a hazardous chemical such as DDT can be limited. Finally, the limited release of certain materials in industrial effluents can be permitted. This option is usually pursued in the case of complex mixtures such as auto exhaust, the release of which is limited by means of catalytic converters. The second and third options underscore the fact that regulation does not necessarily stipulate total elimination; instead, it may involve the adjustment of chemical levels in the environment as a function of need. This, of course, is in accordance with the philosophy of risk-benefit analysis. In many instances, regulatory agencies simply recommend that the levels or uses of hazardous compounds be limited.

METHODOLOGY FOR CRITERIA DERIVATION

Either directly or indirectly, all of the issues discussed previously were involved in the development of the 65 Consent Decree Water Quality Criteria Documents (Table 4). Procedurally, the documentation process entailed an in-depth world literature review. The resulting information was used in generating four chapters that relate directly to mammalian toxicology and human health effects. Critical peer review by

250-300 scientists representing the governmental, academic, and industrial communities ensured the quality and objectivity of these documents.

Table 4

THE 65 CONSENT DECREE WATER CRITERIA DOCUMENTS

Acenaphthene
Acrolein
Acrylonitrile
Aldrin/Dieldrin
Antimony
Arsenic
Asbestos
Benzene
Benzidine
Beryllium
Cadmium
Carbon Tetrachloride
Chlordane
Chlorinated Benzenes
Chlorinated Ethanes
Chlorinated Napthalene
Chlorinated Phenols
Chloroalkyl Ethers
Chloroform
2-Chlorophenol
Chromium
Copper
Cyanide
DDT
Dichlorobenzene
Dichlorobenzidine
Dichloroethylenes
2,4-Dichlorophenol
Dichloropropanes/penes
2,4-Dimethylphenol
2,4-Dinitrotoluene
Dioxins (TCDD)
Diphenylhydrazine
Endosulfan
Endrin
Ethylbenzene
Fluoranthene
Haloethers
Halomethanes
Heptachlor
Hexachlorobutadiene (HCBD)
Hexachlorocyclohezane
Hexachlorocyclopentadiene
Isophorone
Lead
Mercury
Napthalene
Nickel
Nitrobenzene
Nitrophenols
Nitrosamines
PAH's
PCB's
Pentachlorophenol
Phenol
Phthalate Esters
Selenium
Silver
Tetrachloroethylenes
Thallium
Toluene
Toxaphene
Trichloroethylenes
Vinyl Chloride
Zinc

The first chapter dealt with sources and levels of exposure as well as estimates of total exposure and body burden. In most cases, levels of pollutants in ambient waters were lower than recommended criteria. In some cases, however, pollutant levels in ambient waters were found to be greater than the criteria due either to natural background or anthropogenic releases. Theoretically, criteria are levels of pollutants protective of human health. Economic, social, and political considerations must also be addressed in the promulgation of standards.

The second chapter focused upon relevant pharmacokinetic parameters. Whenever sufficient data were available, they were used in the derivation of criteria. Additionally, pharmacokinetic information provided guidance in the identification of target organs, physiological half-times, and areas for future research.

All toxic effects associated with acute, subchronic, and chronic exposure were reviewed in the third chapter. These effects include: toxicity (acute, subacute, and chronic), teratogenicity and other reproductive effects, mutagenicity, carcinogenicity, and synergism. The most pertinent toxic effects were discussed in relation to criteria derivation in chapter four.

The fourth chapter of the human health effects section specifically addressed the derivation of criteria. Ambient water quality criteria are based on three possible types of biological endpoints: carcinogenicity, toxicity (i.e., all adverse effects other than cancer), and organoleptic effects. As discussed above, carcinogenicity is regarded as a nonthreshold phenomenon. Therefore, safe or no-effect levels for carcinogens cannot be established because any dose must be assumed to elicit a finite response.

For compounds that do not manifest any apparent carcinogenicity, the threshold assumption is used in deriving a criterion. This assumption is based on the premise that a physiological reserve exists within the organism and must be depleted before clinical disease ensues.

In some instances, criteria are based on organoleptic characteristics such as thresholds for taste or odor. These criteria are established when insufficient information is available on toxicity or when the criterion based on organoleptic effects is lower than the level calculated from toxicologic data. It should be recognized that criteria based solely on organoleptic effects do not necessarily represent approximations of acceptable risk levels for human health (4).

Several ambient water quality criteria documents deal with classes of compounds that include chemicals exhibiting varying degrees of structural similarity. Prediction of biological effects based solely on structural parameters is difficult; therefore, the derivation of compound-specific criteria is preferable to a class criterion. For members of some chemical classes, however, compound-specific criteria cannot be derived based on available data on one member of a class.

Cancer

After the decision has been made that a compound has the potential to cause cancer in humans and that data exist to permit the derivation of a criterion, the water concentration associated with a lifetime carcinogenic risk of 10^{-5} is estimated. The data used for quantitative estimates are of two types:

- Lifetime animal studies, and
- Human studies where excess cancer risk has been associated with exposure to the agent.

The procedure for deriving water concentration from animal studies is the improved multi-stage model developed by Crump (5) and certain techniques developed by the US EPA (45 FR 79350).

If human epidemiologic data and sufficiently valid exposure information are available for the compound, the data are analyzed by an alternate procedure to give an estimate of the linear dependence of cancer rates based upon the calculated lifetime average dose. If the epidemiology data show no carcinogenic effect when positive animal evidence is available, it is assumed that a risk exists but is smaller than could have been observed in the epidemiologic study. An upper limit of the cancer incidence is calculated, assuming that the true incidence is just below the level of detection in the cohort studies. In human studies, the response is measured in terms of excess risk of the exposed cohort of individuals compared to the control group. In the analysis of these data, it is assumed that the excess risk is proportional to the lifetime average exposure and that it is the same for all ages (45 FR 79350).

Both of these procedures yield slopes termed $q_1^*(A)$ or B_H, respectively. Since $q_1^*(A)$ is derived from animal studies, it must be adjusted to yield an equivalent human slope, $q_1^*(H)$, by the following equation:

$$q_1^*(H) = \frac{[q_1^*(A)]\,[(mg/kg/d)^{-1}]}{(le/Le)\,(Le/L)^3}\sqrt[3]{\frac{70\ kg}{w(kg)}} \qquad (1)$$

where:

$q_1^*(A)$ = the upper 95% estimate of the linear component of the slope (potency factor) estimated from all the animal data;

le = the length of exposure;

Le = the length of the experiment;

L = the lifespan of the animal; and

w = average weight of the animal.

The $(Le/L)^3$ factor penalizes the calculation of $q_1^*(H)$ from less than lifetime animal studies. For example, if a study lasted only one-half the normal lifespan of the animal, then, $(1/2)^3 = 1/8$. This value causes an eightfold increase in the value of $q_1^*(H)$ over what it would be if Le and L were equal.* The rationale for the use of this factor is documented elsewhere (45 FR 79350) but is based on the concept established by Druckrey (6) that time is more important than dose rate in a carcinogenesis experiment. The cube root of the body weight ratios is a further refinement of the $q_1^*(A)$ potency factor and is based on the suggestion of Mantel and Schneiderman (7) that it represents an equivalent dose among species.

After the slopes describing carcinogenic potency in humans have been calculated, the intake (I) associated with a specific risk (usually 10^{-5} or 1 in 100,000) over a human lifetime is determined:

$$I(\text{mg/d}) = \frac{70\ \text{kg}(10^{-5})}{[q_1^*(H)][(\text{mg/kg/d})^{-1}]} \quad \text{or} \quad \frac{70\ \text{kg}(10^{-5})}{B_H(\text{mg/kg/d})^{-1}} \ . \qquad (2)$$

For this calculation, the average weight of a man is assumed to be 70 kg. The ambient water quality criterion is a straightforward calculation:

$$C(\text{mg}/\ell) = \frac{I(\text{mg/d})}{(2\ \ell/\text{d}) + \{[0.0065\ \text{kg/d}][\text{BCF}(\ell/\text{kg})]\}} \ . \qquad (3)$$

The assumed average daily consumption of water and fish for a 70-kg man is 2 liters per day and 0.0065 kilograms per day, respectively. BCF is the bioconcentration factor of the chemical in liters per kilogram.

Toxicity

In developing guidelines for deriving criteria based on noncarcinogenic responses, five types of response levels are considered:

- NOEL - No-Observed-Effect Level,
- NOAEL - No-Observed-Adverse-Effect Level,
- LOEL - Lowest-Observed-Effect Level,
- LOAEL - Lowest-Observed-Adverse-Effect Level,
- FEL - Frank-Effect Level.

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* Higher values of $q_1^*(H)$ are associated with lower and, therefore, more protective criteria.

Adverse effects are defined as any effects that result in functional impairment and/or pathological lesions that may affect the performance of the whole organism or that reduce an organism's ability to respond to an additional challenge. Frank effects are defined as overt or gross adverse effects (severe convulsions, lethality, etc.).

These concepts are illustrated in Figure 2. They have received much attention because they represent landmarks that help to define the threshold region in specific experiments. Thus, if an experiment yields a NOEL, a NOAEL, a LOAEL, and a clearly defined FEL in relatively closely spaced doses, the threshold region has been relatively well defined. Such data are very useful in deriving a criterion. On the other hand, a clearly defined FEL is of little use in establishing criteria when it stands alone because such a level gives no indication of how far removed it is from the threshold region. Similarly, a free-standing NOEL has little utility because there is no indication of its proximity to the threshold region.

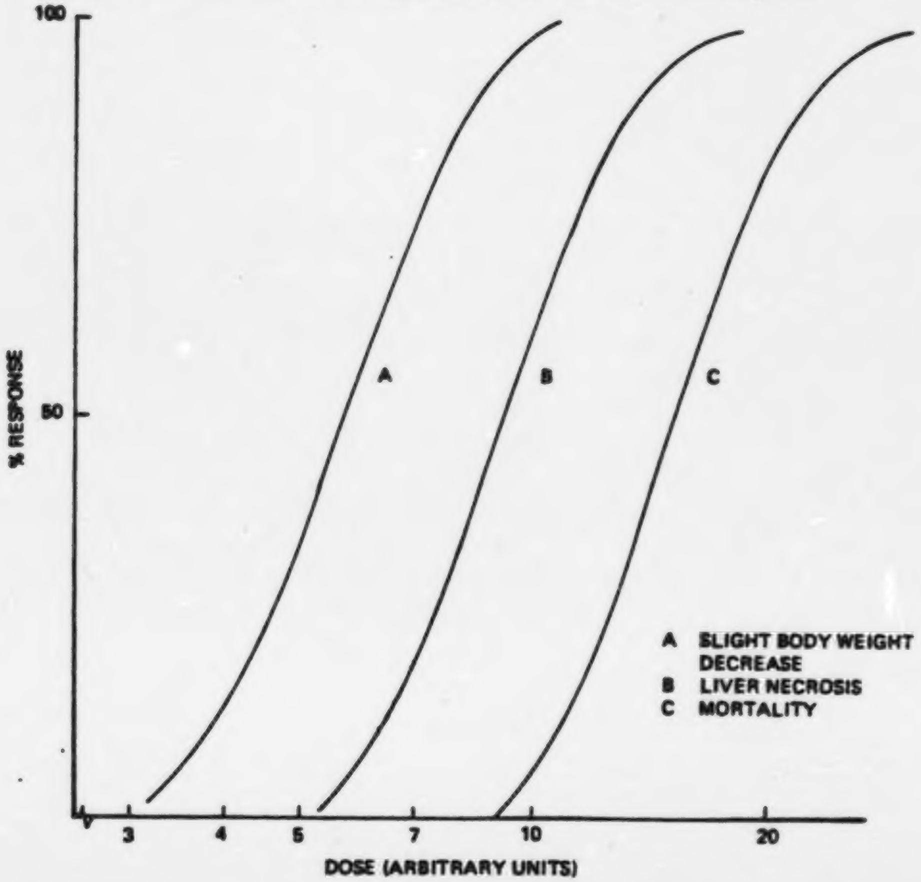

Figure 2. Response levels considered in defining threshold regions in toxicity experiments. Doses associated with these levels are as follow: 3 - NOEL, NOAEL; 4 - LOEL, NOAEL; 5 - NOAEL (Highest); 7 - LOAEL; 10 - FEL; 20 - FEL.

Based on the above dose-response classification system, the following guidelines for deriving criteria from toxicity data have been adopted.

- A free-standing FEL is unsuitable for the derivation of criteria.
- A free-standing NOEL is unsuitable for derivation of criteria. If multiple NOELs are available without additional data on LOEL's, NOAEL's, or LOAEL's, the highest NOEL should be used to derive a criterion.
- A NOAEL, LOEL, or LOAEL can be suitable for criteria derivation. A well-defined NOAEL from a chronic (at least 90-day) study can be used directly, applying the appropriate uncertainty factor. For a LOEL, a judgment must be made as to whether it actually corresponds to a NOAEL or a LOAEL. In the case of a LOAEL, an additional uncertainty factor is applied; the magnitude of the additional uncertainty factor is judgmental and should lie in the range of 1 to 10. Caution must be exercised not to substitute Frank-Effect Levels for Lowest-Observed-Adverse-Effect Levels.
- If--for reasonably closely spaced doses--only a NOEL and a LOAEL of equal quality are available, the appropriate uncertainty factor is applied to the NOEL.

In using this approach, the selection and justification of uncertainty factors are critical. The basic definition and guidelines for using uncertainty factors has been given by the National Academy of Science (3). "Safety factor" or "uncertainty factor" is defined as a number that reflects the degree or amount of uncertainty that must be considered when experimental data in animals are extrapolated to man. When the quality and quantity of experimental data are satisfactory, a low uncertainty factor is used; when data are judged to be inadequate or equivocal, a larger uncertainty factor is used. In those cases where the data do not completely fulfill the conditions for one category--or appear to be intermediate between two categories--an intermediate uncertainty factor is used. Such an intermediate uncertainty factor can be developed based on a logarithmic scale (e.g., 33 being halfway between 10 and 100 on a logarithmic scale).

The actual procedure for calculating the ambient water quality criteria based on toxicity data is quite simple. The chosen effect level in milligrams per kilogram per day (mg/kg/d) from the animal study is divided by the appropriate uncertainty factor. This is multiplied by 70 kg (the standard weight of a man) to yield an acceptable daily intake (ADI); then, the criterion (C) is calculated by an equation similar to Equation (3) with the standard assumptions of water and fish consumption as previously mentioned.

$$C(\text{mg}/\ell) = \frac{\text{ADI}(\text{mg/d})}{(2\ \ell/\text{d}) + \{[0.0065\ \text{kg/d}][\text{BCF}(\ell/\text{kg})]\}} \quad . \qquad (4)$$

Organoleptic

Criteria based upon organoleptic effects are intended to protect against adverse appearance, taste, and/or odor qualities in ambient water. While these criteria do not necessarily represent safe levels of exposure for man because they are not based on toxicity data, they may provide guidance to regulatory agencies in the promulgation of standards. In the event that the organoleptic effect level is below the level responsible for health effects, they can be used as the basis for recommending an ambient water quality criterion.

EXAMPLES

Cancer

The study of Preussman et al. (8) is an example of the basis of a cancer-based criterion. Sprague-Dawley rats of both sexes were administered N-nitrosopyrrolidine at one of several drinking water concentrations equivalent to 0, 0.3, 1.0, 3.0, or 10 mg/kg/body weight/day throughout life. The corresponding incidences of various malignant tumors were 6, 12, 20, 32, and 11%, respectively.

An estimated value of 0.364 $(\text{mg/kg/d})^{-1}$ for $q_1{}^*(A)$ was derived from these data using the multi-stage model as previously described (5). The equivalent human potency factor is then calculated by Equation (1):

$$q_1{}^*(H) = \left[\frac{0.364\ (\text{mg/kg/d})^{-1}}{(728\ \text{d}/728\ \text{d})(728\ \text{d}/728\ \text{d})^3}\right]\left[\sqrt[3]{\frac{70\ \text{kg}}{0.350\ \text{kg}}}\right]$$

$$= 2.13\ (\text{mg/kg/d})^{-1} \quad .$$

The daily intake associated with a 10^{-5} cancer risk is determined by Equation (2):

$$I = \frac{70\ \text{kg}(10^{-5})}{2.13(\text{mg/kg/d})^{-1}}$$

$$= 0.329\ \mu\text{g/d} \quad .$$

The ambient water quality criterion is found by Equation (3):

$$C = \frac{0.329\ \mu g/d}{(2\ \ell/d) + [(0.0065\ kg/d)(0.055\ \ell/kg)]}$$

$$= 164\ ng/\ell\ .$$

Toxicity

The study of MacKenzie, et al. (9) is an example of the basis for a toxicity-based criterion. Sprague-Dawley albino rats of both sexes were given chromium VI as potassium chromate at one of several drinking water concentrations (0, 0.45, 2.2, 4.5, 7.7, 11, or 25 mg/ℓ) for one year. No effects were noted at the six lowest doses. The highest dose (25 mg/ℓ) caused a decreased water intake.

For purposes of criterion derivation, the highest dose can be considered a well-defined NOAEL (the lower doses are NOEL's). Furthermore, it is considered that the 25 mg/ℓ concentration represents exposure from chromium alone. An ADI can be calculated from this NOAEL as follows:

$$\frac{[25\ mg/\ell\ (NOAEL)][0.035\ \ell/d]}{0.350\ kg} = 2.5\ mg/kg/d\ ,$$

$$ADI = \frac{(2.5\ mg/kg/d)(70\ kg)}{1,000} = 0.175\ mg/d\ .$$

Where 0.035 ℓ/d is the assumed average daily water consumption and 0.350 kg is the assumed average body weight of rats in the study, 1,000 represents the uncertainty factor employed per NAS guidelines (3) and 70 is the assumed average weight of a man.

A protective level is calculated using Equation (4):

$$C = \frac{0.175\ mg/d}{(2\ \ell/d) + [(0.0065\ kg/d)(16\ \ell/kg)]} = 83\ \mu g/\ell\ .$$

Based on these calculations, the US EPA recommended the previous standard for total chromium, 50 µg/ℓ (10), as the ambient water quality criterion for chromium VI. The above calculations were judged supportive of the standard but insufficient to warrant changing it.

SUMMARY

From the foregoing discussion, it is clear that agencies involved in environmental regulation are confronted with a complex constellation of issues. The magnitude of risks posed by the three biological endpoints that were used as a basis for criteria derivation (i.e., carcinogenicity, chronic toxicity, and organoleptic effects) are determined ultimately by the levels of the compounds in the environment. Similarly, the compartment(s) of the ecosystem in which a contaminant resides will often determine which agency or agencies will bear primary responsibility for regulation.

From a practical point of view, the greatest difficulty to be dealt with by regulatory agencies is the inadequacy of the toxicological data base. Long-term studies in experimental animals should constitute a primary focus of future research for hazardous chemical pollutants. Without such basic data, the scientific community will be hard pressed to make firm or defensible recommendations for the protection of human health.

This need is, of course, complicated by economic considerations. The cost of augmenting the chronic toxicity data base for chemicals included in the 65 Consent Decree documents is at least 50 million dollars. If all other commercially significant chemicals were considered, the cost would be much more. Consequently, regulators, in concert with the scientific community, must develop a rational scheme for determining research priorities. In toxicology, this need is being partially addressed by the proliferation of screening tests for carcinogenicity. Although these tests certainly have merit, they have yet to be extensively validated.

Until toxicologists can provide reliable and economic screening procedures, we must--to a great extent--rely upon environmental chemists. Chemical monitoring data provide reasonably precise estimates of chemical prevalence and current levels of human exposure and should be considered in assessing research needs. While prevalence and persistence do not necessarily indicate hazard, it is clear that biological testing should emphasize hazard assessment for those chemicals to which the human population is most extensively exposed.

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QUESTIONS AND ANSWERS

Q: As I understand it, you've said that in developing standards the states will utilize the criteria as guidance input. Has EPA done any work to provide model analyses for the states to set regulations, or will this be left up to the states entirely?

A: I think Joe Cotruvo could probably answer the question better than I; however, I know that the federal representatives from the Water Quality Office and the state people plan to get together. Fortunately, they asked that we be involved along with the Cancer Assessment Group. The issue of state standards will be the subject of detailed review at these meetings.

Q: What about the role of state advisory groups? I alluded to them earlier this morning. Can you tell us what you think some of the major topics for analysis by these groups will be and how you see them helping the states in setting regulations?

A: The only contacts we had were with a planning group in the state of Michigan. I am not aware of how many preliminary meetings the Office of Water Quality held with other state representatives.

Q: What is the basis of the National Academy of Science's safety factors and its relationship to the acceptable daily intake?

A: The recommended safety factors, or to use a better term, uncertainty factors, were published in *Drinking Water and Health* by the National Academy of Science in 1977. The monograph also discussed the reasons why the safety factors are to be used. In my talk, I have presented a summary of the recommended approach. The NAS recommends the use of uncertainty (safety factors) of 10, 100 or 1000 to provide for the uncertainty inherent in reported epidemiological and toxicological data. This procedure was recommended by a Committee of the National Academy of Sciences and our scientific groups considered this to be a useful approach. Accordingly, we have adopted their use in our Methodology for the Water Quality Criteria Documents. The Acceptable Daily Intake for a chemical is then calculated using the formula I have presented which includes the application of the appropriate uncertainty factor.

Q: As for state standards, what do you envision as the number of standards that would have to be set in terms of the priority pollutants? Will the states have to set numerical standards for each one of these, for a certain percentage, or what?

A: To my knowledge, the present official position is that US EPA will recommend a list of pollutants to the states for which standards should be considered. Some of the pollutants may not be considered because the data base is not as strong as we would like it to be. In addition, using the linear model, some of the criteria levels may be very low. Yet, as Dr. Albert said, we have used the nonthreshold linear approach for carcinogenic chemicals. To explain this further, when this model is used we estimate an incremental risk to the population due to intake from water and contaminated fish over a 70-year period. There is a possibility that either natural or anthropologic background levels of the pollutant measured in ambient water may in some instances have been higher than the calculated criteria level.

I must emphasize that the derived criteria correspond to levels of pollutants in bodies of water which represent an estimate of incremental risk for carcinogens and "no effect levels" for noncarcinogens, and which may--at times--be lower than reported concentrations of the pollutants in some areas. The criteria are intended to be protective of human health without regard to present levels in water. It should be our goal to reduce pollution levels accordingly, even though--at the present time--we are unable to accomplish it. This is why the criterion is only one of the factors that must be considered in setting the state standards.

Q: I still have one problem that I think is going to be a consistent problem: How do we know what is a good animal study and what's a marginal animal study? What is an intermediate study? When do we divide by 100, or 1,000, or 10,000? These criteria are not explicit and have never really been addressed. I would think that we would have to do something about this in the future.

A: Let me just say that we had 8 or 10 expert scientists to review each document. Three or four were scientists who had published extensively on that particular chemical and can be called experts. Two or three had expertise in the general areas of epidemiology or toxicology; and one or two had expertise in cancer research. That is how our review committees were usually formed. In addition to this, there were several government scientists who had an intimate knowledge of the pollutant and of the related regulatory approach. The Committee made the best possible judgments, yet I agree that there were--at times--unanswered questions, and yours is one of them. Often scientific judgment is important along with the data in resolving these issues. This is why I am satisfied that our group will be involved in the discussions concerning setting of standards. We know which data are satisfactory and where there are some gaps in knowledge.

Q: To carry Tony Colucci's comment one step further, tell us how you cope at present with conflicting results from different studies? What method do you have to resolve this? For example, suppose you have animal studies with conflicting results; one lab shows a positive effect and another lab shows a negative effect. What do you do?

A: That's another good question, and I will give a very simple answer. If two studies are comparable in quality and only one showed a positive effect, we would use the positive study because, in studies with 20-100 animals, you cannot dismiss the statistical probability that the negative data are equivocal. For example, in the case of trichloroethylene, one NCI bioassay study demonstrated carcinogenic effects in mice. Yet the studies of Van Duuren and Maltoni are reported to be negative. Can a regulatory agency contradict the NCI data? Can we brush the NCI study under the rug--especially if it deals with a carcinogenic response? In case of toxicity data, there are often discrepancies among various studies; however, since these are threshold agents, the judgments concerning conflicting effect data may be resolved more easily. But in the case of carcinogens, we must be extremely careful.

Q: What is the state of the data that you need before you consider it? Must it appear, for example, in peer review journals?

A: Yes. At times, if we need further details, we may call the researcher either to confirm the published data with additional information or, in case of a continuing research project, we may be interested if the new data clarified the gaps in information. Normally, however, we would use peer reviewed journal articles almost exclusively.

Q: Do you always use the most sensitive response with noncarcinogens?

A: No.

Q: How do you decide?

A: Sometimes we may use a LOEL instead of a NOAEL. In other words, we use the lowest-observable-effect-level if the study has a greater degree of reliability than the study that suggested a NOAEL. We do not like to use a NOEL because this factor usually represents an undefined number. In contrast, a NOAEL is usually rather well defined.

Q: I was referring to qualitatively different kinds of responses. For example, if you have an enzyme impairment as the most sensitive, there's a real question as to whether or not that had any toxicological consequences.

A: In our methodology, we have described the types of effect data to be used; they are based on functional effects and/or pathological lesion effects. At times, biochemical effect data were used but only those that are of generally recognized significance.

Q: Why doesn't EPA require peer review in research they do themselves? Sometimes they issue documents that have no peer review at all.

A: This is possible. However, the scientific documents issued by ECAO-CIN, which is my group, are all subjected to peer review.

The Multistage Model With a Time-Dependent Dose Pattern: Applications to Carcinogenic Risk Assessment[1]

(Abbreviated Title: Cancer Model with Time-Dependent Dosing)

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[1] This research was supported by EPA Contract 68-01-3111. It has not been reviewed by EPA.

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Key Words: cancer, risk assessment, multistage model, exposure pattern.

A cancer risk assessment methodology based upon the Armitage-Doll multistage model of cancer is applied to animal bioassay data. The method utilizes the exact time-dependent dose pattern used in a bioassay rather than some single measure of dose such as average dose rate or cumulative dose. The methodology can be used to predict risks from arbitrary exposure patterns including, for example, intermittent exposure and short-term exposure occurring at an arbitrary age. The methodology is illustrated by applying it to a National Cancer Institute bioassay of ethylene dibromide in which dose rates were modified several times during the course of the experiment.

I. Introduction

In the Armitage and Doll(1) multistage model of cancer, it is assumed that a cell line goes through k distinct stages in its progression to becoming cancerous. The rate at which it progresses through the ith stage is assumed to be a constant λ_i. Different cell lines are assumed to compete independently in producing tumors. This simple model predicts that cancer incidence will increase as $(\text{age})^{k-1}$, which agrees with the observation that the age-specific incidence rates of many human cancers--particularly carcinomas in organs other than sex organs--increase as $(\text{age})^x$ where x ranges between 3 and 6.(2-3)

The Armitage and Doll model has been extended to include the effect of exposure to a carcinogen by assuming that the transition rate at which a cell goes through each stage is linearly related to the dose rate, i.e., that

$$\lambda_i = \alpha_i + \beta_i d \qquad (1)$$

where d is the dose rate of a continuously applied carcinogen.(4) Here α_i is the background transition rate in the absence of an applied dose, and β_i represents the increase in the transition rate per unit dose. An equivalent assumption is that the residence time of a cell in each stage has an exponential distribution with mean $1/\lambda_i$. With this formulation the probability of a cancer by age t is approximately of the form

$$P(d,t) = 1 - \exp[-ct^k \prod_{i=1}^{k} (\alpha_i + \beta_i d)] \qquad (2)$$

where c is a constant that does not involve d, t, or any of the α's or

β's.(4) For a fixed age t, the exponent in this expression is a polynomial in the dose rate d. This polynomial form prompted Guess and Crump(5) to recommend a model for carcinogenic risk assessment from animal data of the form

$$P(d) = 1 - \exp(-q_0 - q_1 d - \ldots - q_k d^k) \qquad (3)$$

where $q_i \geq 0$. Here P(d) represents the probability of cancer by a fixed time--typically the time at which the experiment is terminated. This model, along with related statistical methods,(6-10) has been used by the EPA and other regulatory agencies to assess low dose cancer risks.(11-12) Although expression (3) has been called "multistage model," it actually is more general than (2) with t fixed, because the exponent in (3) contains polynomials not predicted by (2).

Whittemore and Keller(13) developed expressions for the Armitage-Doll model which apply when the dose rate is not constant throughout life. Day and Brown(14) extended this work and developed expressions for the cancer patterns predicted by the multistage model when exposure occurs early or late in life and when different stages in the carcinogenic process are affected by the exposure. Comparing the cancer patterns predicted by these expressions with experimental and epidemiological data, they concluded that some of the known carcinogens appeared to affect early stages ("early stage carcinogens") while others affected late stages ("late stage carcinogens").

The purpose of the present paper is to develop further the model studied by Whittemore and Keller and by Day and Brown, and to consider its use in predicting carcinogenic responses to different dose patterns. In particular, methods are developed and illustrated for applying the model to data from animal bioassays in which the administered dose rate changes during the course of the experiment, and for developing estimates of risks from time-dependent exposure patterns which are possibly different from those used in the bioassay, but change with time. A similar method was recently proposed by Thorslund.(15)

Dose rates are often changed during the course of a bioassay, although the changes often are not part of the original protocol. For example, the higher experimental dose rates are sometimes lowered if they appear to be causing acute toxicity. Likewise, dose rates are sometimes increased during a study if it appears that the animals could tolerate higher dosages. Some studies have variations in dose rates as part of their original protocol. For example, some protocols specify that dosing be terminated after about 1/2 of the animals' normal lifespans have elapsed.(16) In other studies, animals are given only a single dose at the beginning of the experiment.(17) Some studies (e.g., the ED_{01} study of 2-AAF)(18) utilize different patterns of dose rates for the express purpose of studying the effect of these patterns upon carcinogenic response.

Any changes in the dose rate during the experiment, whether part of the original protocol or not, complicate the analyses of the studies, particularly if the analyses involve quantitative assessment of risk. Some type of average dose rate typically is used as the dose measure for purposes of risk assessment. However, this can give misleading results because all doses are not equivalent; a dose applied early in life can have a different effect than the same dose applied later, depending upon the nature of the carcinogenic process. The procedures developed in this paper offer a means of dealing with this situation within the framework of the multistage model. They utilize the exact dosing pattern, rather than an average dose rate. They also can be used to estimate risks under different exposure patterns than those utilized in the experiment.

II. Basic Properties of the Armitage-Doll Model

If the dose rate is not constant, then equation (1) is modified by replacing the average dose rate d, by the instantaneous dose rate D(t), where D(t) is the dose rate to which an animal is exposed at age t. One consequence of this assumption is that a carcinogen can have an effect only when it is being administered. This is probably not a valid assumption for chemicals which are stored in body fat and then released slowly into the systemic circulation. For this reason and others, when applying the model, it would be more appropriate to interpret D(t) as internal dose at the site of action, rather than as externally administered dose.

For an arbitrary dose pattern D(t), if several stages are dose-related, the carcinogen response predicted by the multistage model has an extremely complicated form. In the Appendix we have derived exact expressions for the probability of a carcinogenic response by age t, for the special cases in which either 1 or 2 stages out of k are affected by the carcinogen and D(t) is a step-function. These special cases are probably adequate for most purposes. Even if more than 2 stages are dose-related, it seems unlikely that there would ever be sufficient data for distinguishing between 2 stages being affected and more than 2. Likewise, any dose pattern D(t) can be approximated arbitrarily closely by a step-function. Besides, dose patterns in most studies are step-functions.

If only the rth stage is dose-related the probability of a carcinogenic response by age t is given by

$$P(t) = 1 - \exp[-q_0(t - \delta)^k - q_r Z_{rk}(t - \delta)] \qquad (4)$$

(see Appendix) where q_0, q_r, and δ are parameters estimated by maximum likelihood (these q's do not have precisely the same meaning as those in (3)). The parameter δ represents a constant delay from cancer initiation to expression. This delay is modeled as a constant for two reasons: Firstly, the variability of this growth period is likely to be much less than those of the initiation stages; secondly, to model realistically this growth period as random would require the estimation of additional parameters. The assumption that does not depend upon dose seems appropriate at least for small doses.(4) The first term in the exponent (4) gives the incidence of spontaneous cancers, and the second term the extra incidence due to the dose pattern D(t). The function Z_{rk} depends, in a complicated manner, upon r, k, and the dose pattern D(t). A similar expression (A23) holds whenever 2 stages are dose-related.

The formulae in the Appendix for constant exposure over a fraction of a lifespan (equations A19-A24) enable us to consider the effect of exposure periods of varying duration and beginning at different ages. Tables 1-3 contain ratios, computed using these formulae, of the extra risk of cancer by age 70 from a partial lifetime exposure at a given level to the extra risk by age 70 from lifetime exposure at the same level.[1] As an example of the interpretation of these tables, consider a 5-stage model and suppose that an individual is exposed from age 20 to age 55 to 10 mg/kg/day of a carcinogen. If only the first stage is affected by the carcinogen, according to Table 1, his additional lifetime risk is estimated to be 0.19 as large as that of an individual exposed to 10 mg/kg/day for life.

These tables indicate that the extra risk from exposure depends quantitatively upon the number of stages, which stage is affected by the carcinogen, the duration of exposure, and the age at first exposure. If the first stage is dose-related, early exposures are more dangerous than later ones; according to Table 1, exposure for the first 35 years of life gives almost the same risk as if the exposure continued throughout life, provided there are at least 3 stages. For example, Table 1 shows that with 4 stages the risk from 35 years exposure gives 94% of the risk caused by lifetime exposure. On the other hand, if the penultimate stage is affected, 20 years of exposure beginning at age 20 gives a higher risk than the same exposure beginning at birth, and either a higher or lower risk than the same exposure beginning at age 40, depending upon the number of stages.

III. Use of the Armitage-Doll Model in Carcinogenic Risk Assessment

We have developed computer programs that fit to bioassay data the Armitage-Doll model with either one or two dose-related stages. The program that utilizes 1 dose-related stage is called A-DOLL1 and the one that utilizes 2 dose-related stages is called A-DOLL2. The number of stages k and which of these are dose-related are supplied by the user. The programs also require, for each animal, the age at death (or the

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[1] These tables actually contain ratios of extra cumulative incidence H_2 (second term in exponent of (4); see Appendix). However at low doses extra cumulative incidence is a close approximation to extra risk.

TABLE 1

RISK AT AGE 70 FROM 35 YEARS OF CONSTANT EXPOSURE EXPRESSED AS A FRACTION OF THE RISK FROM 70 YEARS OF CONSTANT EXPOSURE

Age at Beginning of Exposure	Number of Stages			
	3	4	5	6
	Only First Stage Affected[a]			
	Same total dose			
0	1.75	1.88	1.94	1.97
20	0.71	0.52	0.37	0.26
35	0.25	0.13	0.06	0.03
	Same dose rate			
0	0.88	0.94	0.97	0.98
20	0.35	0.26	0.19	0.13
35	0.13	0.06	0.03	0.02
	Only Penultimate Stage Affected[b]			
	Same total dose			
0	1.00	0.62	0.38	0.22
20	1.37	1.44	1.36	1.22
35	1.00	1.38	1.62	1.78
	Same dose rate			
0	0.50	0.31	0.19	0.11
20	0.68	0.72	0.68	0.61
35	0.50	0.69	0.81	0.89

[a] Calculated using equation A19

[b] Calculated using equation A20

TABLE 2
RISK AT AGE 70 FROM 20 YEARS OF CONSTANT EXPOSURE EXPRESSED AS A FRACTION OF THE RISK FROM 70 YEARS OF CONSTANT EXPOSURE

Age at Beginning of Exposure	Number of Stages 3	4	5	6
	Only First Stage Affected[a]			
	Same total dose			
0	2.22	2.59	2.85	3.04
20	1.00	0.79	0.60	0.44
40	0.27	0.12	0.05	0.02
	Same dose rate			
0	0.64	0.74	0.81	0.87
20	0.29	0.23	0.17	0.13
40	0.08	0.03	0.01	0.006
	Only Penultimate Stage Affected[b]			
	Same total dose			
0	0.69	0.26	0.09	0.03
20	1.43	1.24	0.92	0.64
40	1.18	1.66	1.96	2.10
	Same dose rate			
0	0.20	0.07	0.03	0.01
20	0.41	0.35	0.26	0.18
40	0.34	0.47	0.57	0.60

[a] Calculated using equation A19

[b] Calculated using equation A20

TABLE 3
RISK AT AGE 70 FROM INSTANTANEOUS EXPOSURE EXPRESSED AS A FRACTION OF THE RISK FROM SAME TOTAL DOSE PARCELLED OUT UNIFORMLY OVER 70 YEARS

Age at Beginning of Exposure	Number of Stages			
	3	4	5	6
	Only First Stage Affected[a]			
0	3.0	4.0	5.0	6.0
20	1.5	1.5	1.3	1.1
40	0.55	0.31	0.17	0.09
60	0.06	0.01	0.002	0.0004
	Only Penultimate Stage Affected[b]			
0	0.0	0.0	0.0	0.0
20	1.22	0.70	0.33	0.14
40	1.47	1.68	1.60	1.37
60	0.74	1.26	1.80	2.31

[a] Calculated using equation A22

[b] Calculated using equation A23

time at which a tumor was first observed, if different from the time of death); a parameter related to the tumor status at time of death which specifies what type of contribution the animal is to make to the likelihood function; and the dose pattern to which the animal was subjected. The dose pattern must be a step-function. Generally all animals in a particular treatment group will be subject to the same dose pattern. Using these data the program estimates the parameters $q_0, q_r, \ldots$ and δ, which are described in the Appendix, by the method of maximum likelihood. The user can provide to the programs an environmental exposure pattern (which must also be a step-function), and compute estimates of the extra cancer risk, at various ages, along with corresponding statistical confidence limits, resulting from this exposure pattern. Estimates of a dose scale parameter, and corresponding confidence limits, by which the input dose pattern must be multiplied in order to achieve a given level of extra risk can also be calculated.

The likelihood of the data may be represented as a product

$$L = \prod_i F(t_i) \tag{5}$$

where t_i is a time related to the ith animal and the product runs over all of the animals in the experiment. The F for a particular animal can be of 3 types:

$$F(t_i) = 1 - P(t_i), \tag{6}$$

corresponding to the event of interest not having occurred by time t_i;

$$F(t_i) = P(t_i), \tag{7}$$

corresponding to the event of interest having occurred prior to time t_i; and

$$F(t_i) = p(t_i) = P'(t_i), \tag{8}$$

corresponding to the event occurring at time t_i. Which of these 3 possibilities is used for a particular animal is determined by whether the animal had a tumor, whether the tumor was incidental or fatal, and the event whose probability is being estimated.

The Armitage-Doll probability $P(t)$ may represent either the probability of death from a tumor by time t, or the probability of the occurrence of a tumor by time t (i.e., the probability that a tumor has been observed by time, or that one has occurred that would be detected if a necropsy were carried out). If the probability of death is being estimated, then animals having a fatal tumor contribute a term of the type (8) to the likelihood, where t_i is the time of death, and animals whose death is not caused by a tumor (even though they may have a tumor that is discovered incidentally at death) contribute a term of type (6). This has the drawback that tumors discovered at terminal sacrifice are not counted, even though these tumors may contribute the principal evidence for carcinogenicity. If the probability of the occurrence of a tumor is being estimated, then all animals with tumors contribute a term of the type (7) to the likelihood, and tumor-free animals a term of type (6). However, this analysis could be biased if the treatment has an effect upon longevity. As an example to illustrate the possibility of this bias, suppose there are no competing risks; i.e., all animals must die from cancer. It can be easily shown that in this case the maximum likelihood estimate of $P(t)$ must be 1 for all times, even times prior to the first cancer death.

Thus, both methods of analysis have drawbacks. The situation is further complicated by the fact that in many studies no distinction is made between fatal and incidental tumors. Our approach has been to make analyses using different assumptions about whether tumors are fatal or incidental. If these different analyses are comparable, one can have more confidence in the results.

IV. Application

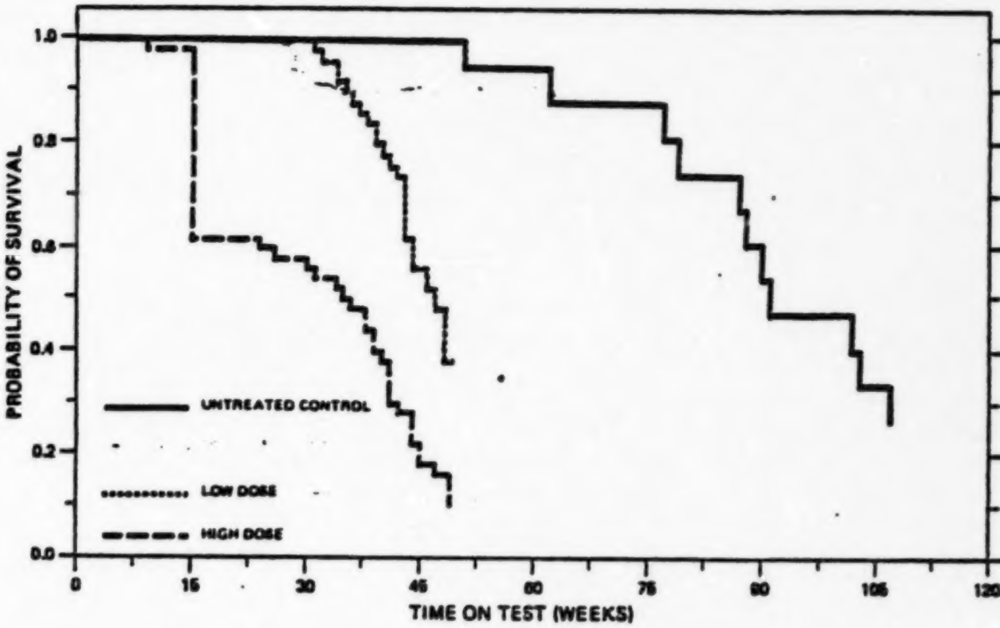
We illustrate the method by applying it to the male rat data from an NCI(19) bioassay of ethylene dibromide (EDB), in which the dosage was interrupted in the high dose group because of high mortality.

Fifty animals were placed into each of a high dose group and a low dose group, and 20 animals were used as vehicle controls. Initially the high and low dose groups received by gavage daily doses of 80 and 40 mg/kg, respectively. However, 19 of the rats in the high dose group had died by the 15th week. Because of this high mortality, dosing to this group was stopped during weeks 16-28. Dosing was resumed at week 29 at the same level applied to the low dose group--40 mg/kg. Dosing was halted in both groups during weeks 42 and 46. All surviving animals were sacrificed by week 63. Figure 1 shows the Kaplan-Meier survival curves for this experiment. Figure 2 shows the dose patterns and the patterns of tumor occurrences in the 2 treatment groups. No tumors of the forestomach were observed in control animals. The high incidence of tumors found during the last week of the study is due to tumors discovered at final sacrifice.

The average doses in the two groups were quite similar--$[(80)(15) + (40)(19)]/49 = 40$ mg/kg in the high dose group and $[(40)(47)]/49 = 38$ mg/kg in the low dose group. However, 45 out of 50 animals in the low

Figure 1

Survival Curves for Male Rats Exposed to EDB



Source: NCI[19]

Figure 2

Male Rats Exposed to EDB by Gavage

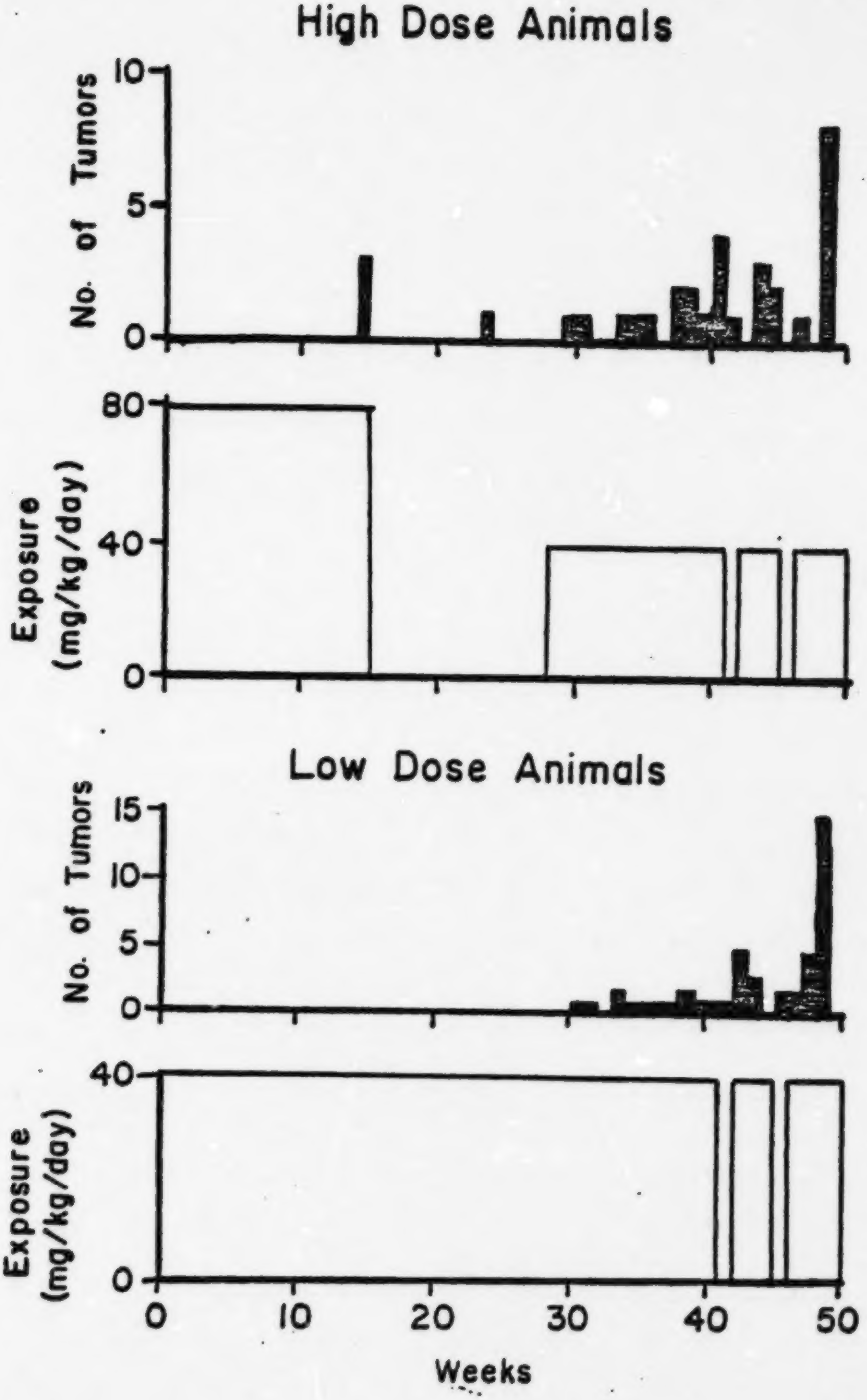


Figure 3a

Comparison of Estimates from Armitage-Doll Model With Kaplan-Meier Estimates: Assumed Six Stages, First Stage Dose Related

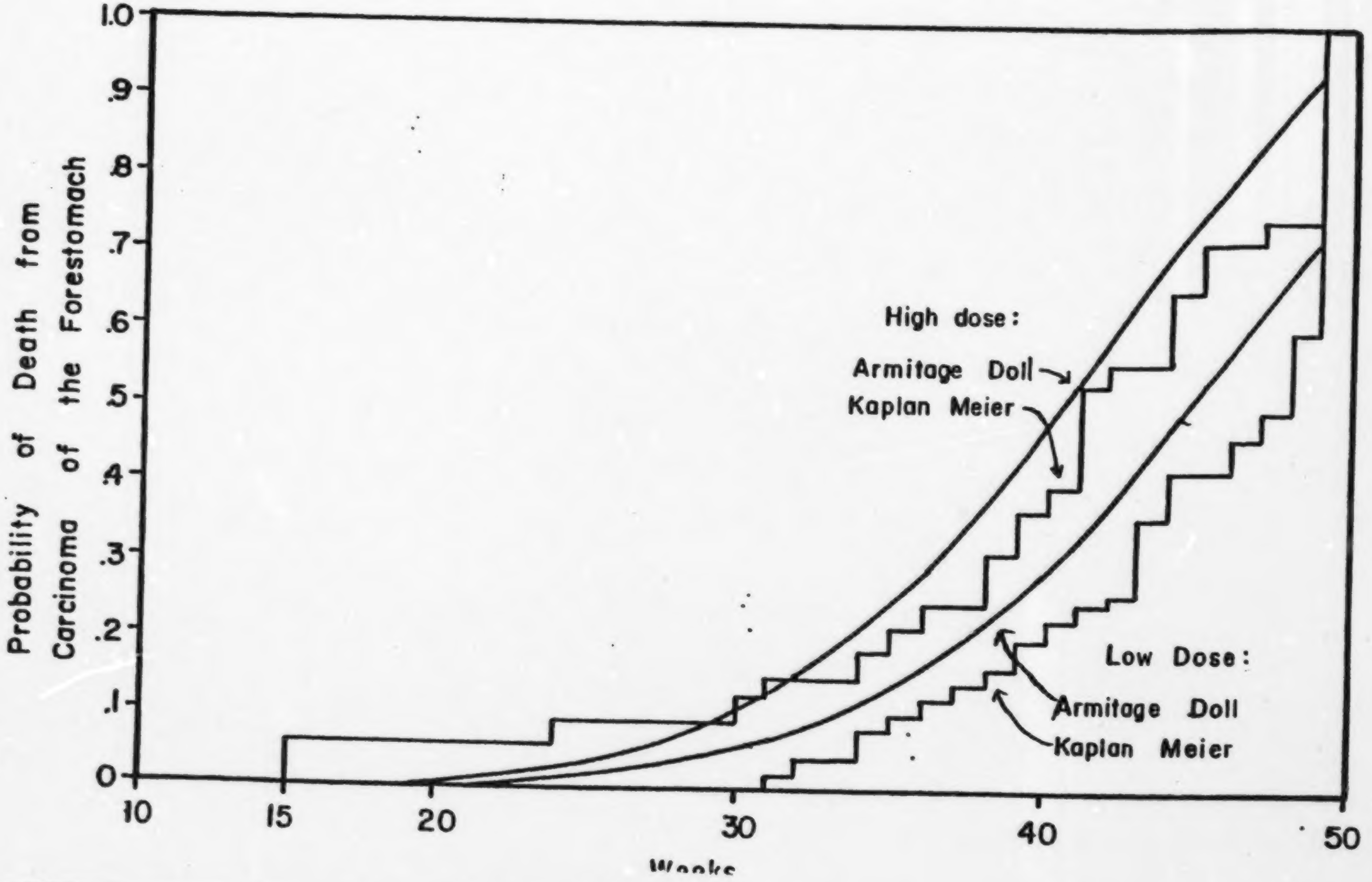
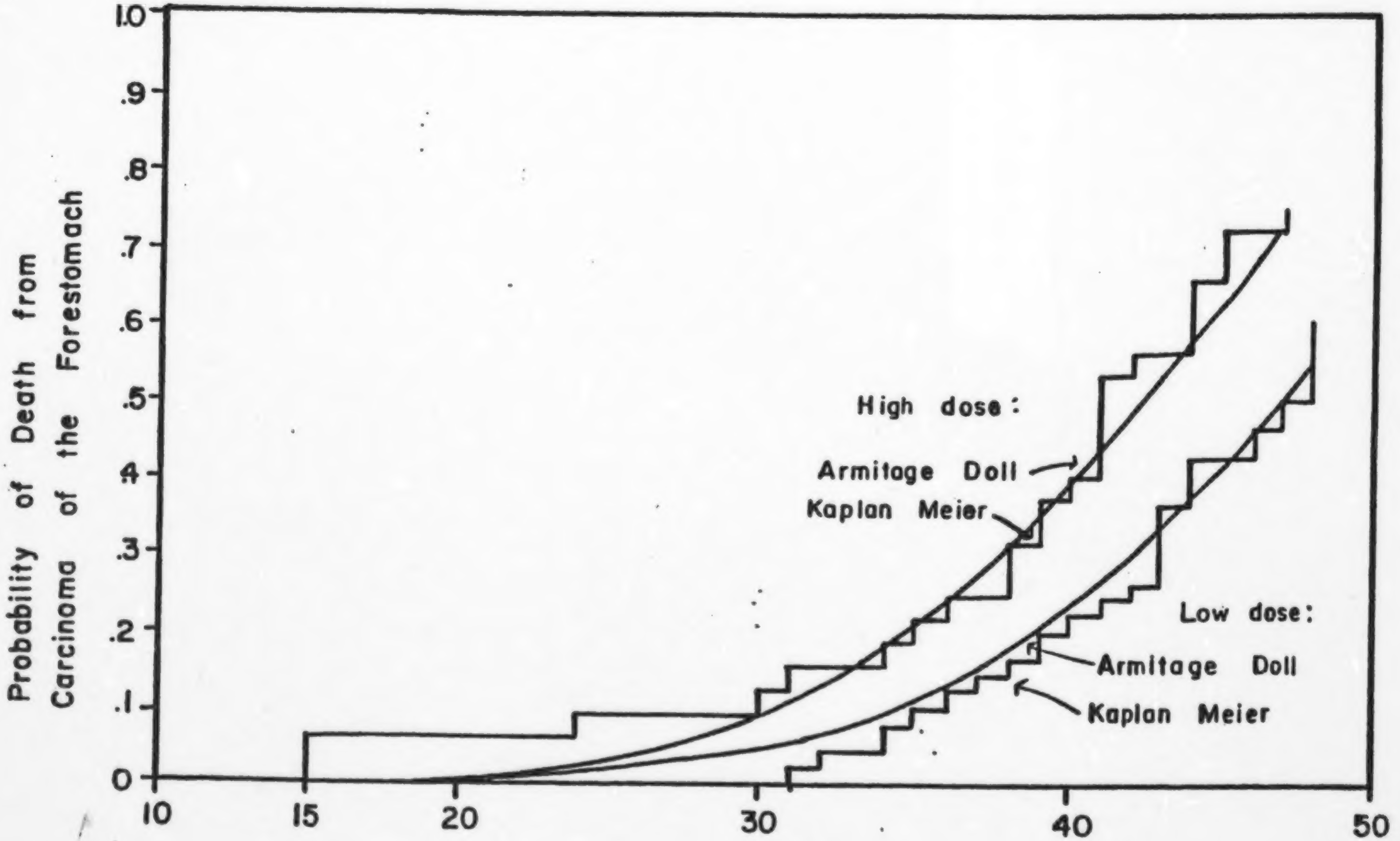


Figure 3b

Comparison of Estimates from Armitage-Doll Model with Kaplan-Meier Estimates:
Assumed Six Stages, First Stage Dose-Related,
Tumors Discovered During Week 49 Omitted



dose group had tumors (squamous-cell carcinoma of the forestomach), as opposed to 33 out of 50 in the high dose group. Clearly, it would be inappropriate to base a risk assessment upon these average doses and total numbers of tumors without taking into account competing risks, the time pattern of tumor occurrences, and the unusual time-dependent dose pattern.

This data set therefore is a candidate for analysis using the Armitage-Doll model. Except for the animals that died during week 15 in the high dose group almost all of the treated animals that died prior to terminal sacrifice had a tumor. However, 4 animals in the low dose group killed at terminal sacrifice were tumor-free. Therefore, it seems likely that most of the deaths prior to terminal sacrifice in tumorous animals were caused by the tumor. Consequently, we decided to focus principally upon analyses in which probability of death from cancer was estimated (i.e., analyses in which all animals with tumors contributed a term of the form (8) to the likelihood). Upon fitting the models using several different assumptions regarding the number of stages k, $1 \leq k \leq 6$, and which single stage was affected by the carcinogen, it appeared that the best fit to the data (fit giving the largest likelihood) was obtained assuming 6 stages with the first stage dose-related.

Figure 3a shows the Kaplan-Meier estimates of probability of death from tumor, considering all deaths without tumors to be censored observations, compared to the corresponding probabilities estimated from the best-fitting Armitage-Doll model ($k = 6$, first stage dose-related). The Kaplan-Meier estimates show that, even though the total crop of tumors is greater in the low dose group, tumors tended to occur earlier in the high dose group, and, after correcting for competing mortality, the estimated probability of response is higher at the high dose than at the low dose for each time point.

The assumption that the tumor caused the death is clearly inappropriate for tumors discovered at terminal sacrifice. To determine how these tumors affected the fit, we refit the data ignoring tumors discovered in week 49. As Figure 3b shows, this improved the correspondence between the Kaplan-Meier curves and the curves derived from the Armitage-Doll model. In fact the fit is excellent except for the difficulty caused by the early cancer-related deaths in the high dose group. There was a large number of tumor-free deaths which occurred at the same time, and it appears likely that these early tumors were not fatal. Although we did not apply a formal goodness-of-fit test, the Armitage-Doll model appears to fit these data quite well.

It should be pointed out that it is appropriate to compare Armitage- Doll and Kaplan-Meier of curves under the assumption that tumors were fatal. However, if tumors had been assumed to be incidental in fitting the Armitage-Doll model (i.e., if animals with tumors had contributed a term of the form (7) to the likelihood) then comparison with the Kaplan- Meier curves would have been inappropriate. Hoel and Walburg(20) graphs of the prevalence of incidental tumors can be used in this circumstance.

Table 4 gives estimates of constant lifetime dose ratios corresponding to extra risks of 10^{-1}, 10^{-2}, and 10^{-4} based upon various assumptions. Both maximum likelihood estimates and lower confidence limits vary approximately linearly with dose. To illustrate the effect of assuming different stages to be dose-related, we considered either the first or third stage to be dose-related. As Table 4 indicates,

TABLE 4

CONSTANT DOSE RATES CORRESPONDING TO GIVEN LEVELS OF EXTRA RISK

	LEVEL OF EXTRA RISK		
MODEL	10^{-1}	10^{-2}	10^{-4}
pr. of death from tumor by week 49; 6 stages; stage 1 dose-related	3.3[a] (2.7)	0.31 (0.26)	(0.0031) (0.0026)
pr. of death from tumor by week 49; 6 stages; stage 3 dose-related	2.5 (2.1)	0.24 (0.20)	0.0024 (0.0020)
pr. of death from tumor by week 49; 6 stages; stage 1 dose-related; tumors found during last week of study omitted	4.7 (3.8)	0.45 (0.36)	0.0045 (0.0036)
pr. of tumor by week 49; 6 stages; stage 1 dose-related	0.91 (0.70)	0.086 (0.067)	0.00086 0.00066
pr. of death from tumor by week 105; 6 stages; stage 1 dose-related; tumors found during last week of study disregarded	0.048 (0.037)	0.0046 (0.0035)	4.6×10^{-5} (3.5×10^{-5})

---

[a] maximum likelihood estimates; 95% lower confidence limits in parentheses.

doses estimated with these 2 approaches differed only by a factor of about 1.3. This suggests that risks estimated from constant dose rates are not extremely sensitive to the particular stage assumed to be dose-related.

Because it is questionable whether tumors discovered at final sacrifice should be used to estimate probability of cancer death, we make estimates both including and excluding tumors found during week 49. The differences in the estimates resulting from these 2 approaches was about a factor of 1.4. However, this difference could be much larger in studies in which nearly all of the tumors are discovered at terminal sacrifice.

We also compared estimates of extra risk of tumor by week 49 with comparable estimates of extra risk of death from tumor by week 49. The former estimates are obtained by using terms of the type (7) rather than (8) in the likelihood. These estimates are probably biased because of the fact that most tumors likely were not discovered incidentally at death, as assumed by the estimating method, but were the cause of death. In spite of this difficulty and the fact that the 2 methods are estimating different quantities, the estimates do not differ greatly; estimates of dose based upon time to tumor are smaller (as could be predicted) by about a factor of 3.5 than comparable estimates based upon time to death from tumor.

NCI rat bioassays typically last about 105 weeks, which is commensurate with the typical rat lifespan. However, because of the high mortality in this study, the terminal sacrifice for male rats took place much earlier. Some adjustment for such a short observation period is needed when estimating lifetime cancer risks. For example, in their methodology for estimating water quality criteria, EPA (1980) adjusted carcinogenic potencies upward by a factor $(L/L_e)^3$ where L is the typical lifespan of the species, and L_e is the duration of the experiment. If the Armitage-Doll model is used for risk estimation, one can estimate the risk at any age, including an age greater than the duration of the experiment. In doing this, one is assuming that the observed response pattern will continue past the period of observation. This calculation is illustrated in the last row of Table 4 which contains estimates of doses corresponding to risks after 105 weeks. These doses are almost exactly a factor of 100 less than the comparable doses estimated for 49 weeks. This is reasonable for a 6 stage model because $(105/49)^6 \approx 100$. Interestingly, if the EPA(11) correction had been used, the factor would have been $(105/49)^3 = 9.8$.

Finally, in Table 5 we examine the effect of a single week of dosing which occurs at either week 1, 14, or 30. It is estimated that a dose given during the 14th week must be about twice as large as that given during the first week to produce the same carcinogenic risk by week 105 and a dose given during week 30 must be about 5 times as large.

V. Discussion

In this paper we have discussed some of the implications of the Armitage-Doll multistage model of cancer to carcinogenic dose risk assessment. We have emphasized particularly the effect of timing of exposure upon cancer risk. The Armitage-Doll model predicts that a particular exposure given early in life will have a greater carcinogenic effect if an early stage is affected by the carcinogen than if a late stage is so affected. We have also presented a new method, based upon this model, for making quantitative risk estimates from animal bioassay

TABLE 5
DOSES OF 1 WEEK DURATION THAT CORRESPONDS TO GIVEN LEVELS OF EXTRA RISK[a]

BEGINNING OF EXPOSURE	LEVELS OF EXTRA RISK 10^{-1}	10^{-2}	10^{-4}
Week 1	0.91[b] (0.69)	0.087 (0.065)	0.00087 (0.00065)
Week 14	1.8 (1.4)	0.17 (0.13)	0.0017 (0.0013)
Week 30	4.7 (3.7)	0.45 (0.35)	0.0045 (0.0035)

---

[a] Extra probability of death from cancer by 105 weeks; tumors found during last week of study disregarded; 6 stages assumed with stage 1 dose-related.

[b] Maximum likelihood estimates; 95% lower confidence limits in parentheses.

data. This method utilizes both the times at which cancers are observed (or at which animals die if cancer-free) and the animals' specific time-patterns of exposure. Using this data one can estimate carcinogenic risk at any age and from under any exposure pattern.

Although we discussed different ways of dealing with the problem of incidental tumors versus fatal tumors, none of these are entirely satisfactory from a theoretical point of view. It appears that this will usually not be a critical issue in light of the many other sources of uncertainty in the risk estimates, since the results obtained from the different approaches ordinarily will not differ appreciably. It should also be kept in mind that similar, but more severe, difficulties are present in estimates made from quantal data, although they are not as apparent.

As is the case with any mathematical model, the multistage model is an idealized representation of a carcinogenic process. It predicts that cancer incidence will vary approximately as age to a power; this relationship is observed for many human carcinogens.(2-3) No particular phenomological interpretation is assumed for the cellular events leading to cancer initiation, although it is reasonable to assume that some of them are mutational in nature. It has recently been demonstrated that 2 point mutations can be involved in human carcinogenesis.(21-22) This suggests a process with at least 2 stages. These point mutations can apparently occur in any order, whereas in the particular multistage model implemented in this paper the stages must be sequential. However, it would not be difficult to consider a version of the model in which the events did not have to occur in a particular order. If the events separating stages are mutations, it would seem reasonable that there would be a linear relationship between internal dose--that is, the dose to the target tissue--and the mutation rates, which is in agreement with the assumption in the multistage model as illustrated in equation (1). For example, if the mutation is an incorrect base substitution the mutation rate should be proportional--at least at low doses--to the number of abberant base molecules available, which in turn should be proportional to the internal dose.

The Armitage-Doll model is more appropriately applied to the dose to the target tissues rather than to the external dose to which the animals are exposed; pharmacokinetic mechanisms relating external dose to tissue dose are not incorporated into the model. Frequently, carcinogenesis dose-response data exhibit a high degree of non-linearity. To achieve this non-linearity within the Armitage-Doll model requires several dose-related stages. It seems likely, however, that most of this non-linearity is due to non-linearity in pharmacokinetic mechanisms(23) rather than in mechanisms of carcinogenesis per se. For example, once non-linearities in uptake are accounted for in an animal bioassay for vinyl chloride the data became consistent with a one-hit model.(24-25) It seems entirely possible that, once the non-linearity in pharmacokinetic mechanisms are accounted for, Armitage-Doll models with a single dose-related stage may be adequate models for most carcinogenesis dose-response data.

There are both observed phenomena associated with particular carcinogens or cancer types, as well as theories of cancer, which are not incorporated into the multistage model. For example, the process of DNA repair is not included in the model, nor is the effect of the immune system. It is possible that the principal effect of DNA repair upon the dose response would be to reduce the rate at which mutations occur. If so, then inclusion of DNA repair in the model would lead to larger estimates of α_i and β_i which would be offset by the effect of DNA repair, but would not substantially affect the overall predictions of the model. If DNA repair or other more detailed mechanistic assumptions were introduced into the model one would have to deal with the problem of estimating additional parameters from data which are possibly already overburdened. A currently popular view of carcinogenesis is that it is an initiation-promotion process. This view could be considered within the multistage approach, with initiation relating to early stages and promotion to later stages.(14) However, the promotion stage--at least as observed in animal skin painting studies--can exhibit regression, with tumors becoming smaller or disappearing altogether when the treatment with a tumor promoter is stopped. This behavior is not modeled in the current model; stages, once attained, are irreversible and lesions are not allowed to regress on their way to becoming cancerous.

Thus the simple multistage formulation in this paper cannot be expected to represent many detailed features of complicated and little-understood carcinogenic processes. However, it is successful in describing many epidemiological and experimental observations. It seems to us to provide a useful framework for investigating the quantitative aspects of time-dependent dosing.

Acknowledgement: The authors would like to express appreciation to Dr. Todd Thorslund and others in the EPA Carcinogen Assessment Group (CAG) for helpful discussions, and for making their related work available to the authors. Although the research described in this article

has been funded by the United States Environmental Protection Agency through contract 68-01-3111, it has not been subject to the Agency's peer and administrative review and therefore does not necessarily reflect the views of the Agency, and no official endorsement should be inferred.

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APPENDIX

A1. Derivation of special cases of the Armitage-Doll model

In the Armitage-Doll model of cancer, a tumor results when k events $w_1,\ldots,w_k$ have occurred in a single cell. Within each cell these events occur in order. Once the first i - 1 events $w_1,\ldots,w_{i-1}$ have occurred, the ith event w_i occurs at the rate $\lambda_i(t)$, where t represents age (not the time since the occurrence of the i-1st event). The dose rate D(t) at age t of a carcinogen is introduced into the model by assuming that

$$\lambda_i(t) = \alpha_i + \beta_i D(t). \tag{A1}$$

The parameter α_i represents the rate at which the ith event occurs in the absence of a carcinogenic insult and is assumed to be age-independent. The parameter β_i represents the carcinogenic potency of the carcinogen upon the ith stage, and is likewise age-independent.

Under these assumptions it can be shown that the probability density of the age at which w_2 occurs in a particular cell is given by

$$f_2(u_2) = \int_0^{u_2} \lambda_1(u_1)\exp[-\int_0^{u_1}\lambda_1(v)dv]\lambda_2(u_2)\exp[-\int_0^{u_2-u_1}\lambda_2(u_1+v)dv]du_1 \tag{A2}$$

$$\equiv \int_0^{u_2}\lambda_1(u_1)\lambda_2(u_2)R_2(u_1,u_2)du_1.$$

The last equality defines R_2. Note that $R_2(u_1,u_2) \longrightarrow 1$ uniformly for $0 \le u_1 \le u_2 \le t$ as $\lambda_1(u_1), \lambda_2(u_2)$ both $\longrightarrow 0$ uniformly in this interval. By induction it can be shown that the probability density of the age at which the ith event w_i occurs in a single cell can be written as

$$f_i(u_i) = \int_0^{u_i}\int_0^{u_{i-1}}\cdots\int_0^{u_2}\lambda_1(u_1)\ldots\lambda_i(u_i)R_i(u_1,\ldots,u_i)du_1,\ldots,du_{i-1}$$

for i = 2,...,k, where (A3)

$R_i(u_1,\ldots,u_i) \longrightarrow 1$ uniformly for $0 \leq u_1 \leq \ldots \leq u_i \leq t$ as $\lambda_1(u_1),\ldots\lambda_i(u_i) \longrightarrow 0$ uniformly. The probability $P_c(t)$ of a cancer in a particular cell line by age t is the integral of the probability density

$$P_c(t) = \int_0^t f_k(u_k)du_k. \qquad (A4)$$

In a tissue comprised of n cell lines acting independently, the probability of a cancer by age t is

$$\begin{aligned} P_n(t) &= 1 - [1 - P_c(t)]^n \\ &= 1 - \exp\{n\mathrm{Ln}[1 - P_c(t)]\}. \end{aligned} \qquad (A5)$$

Since n is typically a very large number, in order that P(t) is a moderate number the probability $P_c(t)$ that cancer results in a particular cell line must be small. One way to express this mathematically (there are many other possibilities that would lead to essentially the same conclusion) is to suppose that α_i and β_i depend upon n in such a way that $\alpha_i n^{1/k} \longrightarrow a_i$ and $\beta_i n^{1/k} \longrightarrow b_i$ as $n \longrightarrow \infty$. It then follows that $\lambda_i(u_i) \longrightarrow 0$ uniformly in any finite interval and thus the limiting process and integration can be interchanged. Using (A3), (A4) and (A5) we get $P_n(t) \longrightarrow P(t)$ as $n \longrightarrow \infty$, where

$$P(t) = 1 - \exp[- H(t)] \qquad (A6)$$

and the cumulative hazard H(t) is given by

$$H(t) = \int_0^t \int_0^{u_k} \cdots \int_0^{u_2} [a_1 + b_1 D(u_1)] \ldots [a_k + b_k D(u_k)] du_1 \ldots du_k. \qquad \text{(A7)}$$

This expression will be our starting point for deriving expressions for P(t) corresponding to various special cases.

A1.1. Case in which a single stage is dose-related: Suppose that the rth stage only is dose-related. This means that $b_r > 0$ for a particular r, $1 \leq r \leq k$ and that $b_i = 0$ for $i \neq r$. Then H(t) can be written as the sum of 2 integrals $H_1(t)$ and $H_2(t)$ where

$$H_1(t) = (\pi a_i) \int_0^t \int_0^{u_k} \cdots \int_0^{u_2} du_1 \ldots du_k = (\pi a_i) t^k/k! \qquad \text{(A8)}$$

represents the background cumulative incidence and

$$H_2(t) = [(\pi a_i)(b_r/a_r)] Z_{rk}(t)/k! \qquad \text{(A9)}$$

represents the extra cumulative incidence due to exposure, where

$$Z_{rk}(t) = k! \int_0^t \int_0^{u_k} \cdots \int_0^{u_2} D(u_r) du_1 \ldots du_k \qquad \text{(A10)}$$

To evaluate $Z_{rk}(t)$, we integrate first with respect to $u_1 \ldots u_{r-1}$, and then--after reversing the order of integration--with respect to $u_k, \ldots, u_{r+1}$. The result is

$$Z_{rk}(t) = \frac{k!}{(k-r)!(r-1)!} \int_0^t D(u_r)(t - u_r)^{k-r} u_r^{r-1} du_r . \qquad \text{(A11)}$$

Applying a binomial expansion to $(t - u_r)^{k-r}$ yields

$$Z_{rk}(t) = \sum_{j=0}^{k-r} \frac{(-1)^j k!\, t^{k-r-j}}{j!(r-1)!(k-r-j)!} \int_0^t D(u_r) u_r^{j+r-1} du_r \qquad \text{(A12)}$$

In order to proceed further we must make more detailed assumptions regarding the dose rate function D(t). It will be sufficient to consider D(t) to be a step-function because any reasonably well-behaved function can be approximated by such a function. Additionally, dose patterns in animal experiments typically are step-functions. Therefore, we suppose that D is the step-function

$$D(x) = h_i, \quad s_{i-1} \leq x \leq s_i \quad . \qquad \text{(A13)}$$

for $i \geq 0$, where $s_0 = 0$. For fixed t, let m satisfy $s_{m-1} < t \leq s_m$. Then

$$\begin{aligned} \int_0^t D(u_r) u_r^{j+r-1} du_r &= \frac{1}{j+r}\left[\sum_{i=1}^{m-1} h_i (s_i^{j+r} - s_{i-1}^{j+r}) + h_m (t^{j+r} - s_{m-1}^{j+r})\right] \\ &= \frac{1}{j+r}\left[\sum_{i=1}^{m-1} (h_i - h_{i+1}) s_i^{j+r} + h_m t^{j+r}\right] \qquad \text{(A14)} \\ &= \frac{1}{j+r}\left[G(j+r, m-1) + h_m t^{j+r}\right] , \end{aligned}$$

where the last equality defines the function G.

Expressions (A6), (A7), (A8), (A10), (A12) and (A14) define a closed form expression for P(t). In the special case m = 1 (constant dose of h_1) this solution reduces to the Weibull form

$$P(t) = 1 - \exp[-h_1(\Pi a_i)(1 + b_r/a_r)t^k/k!] \qquad (A15)$$

just as it should.

In the computer implementation of the model a delay δ is included which represents the period from the initiation of the tumor to its clinical expression. Modifying the definition of P to incorporate this delay, the form of the model implemented by the computer is

$$P(t) = 1 - \exp[-q_0(t - \delta)^k - q_r Z_{rk}(t-\delta)] \qquad (A16)$$

where

$$q_0 = (\Pi a_i)/k! \qquad (A17)$$

and

$$q_r = (\Pi a_i)(b_r/a_r)/k!. \qquad (A18)$$

The computer program obtains maximum likelihood estimates of the 3 parameters of q_0, q_r, and δ, all of which are constrained to be non-negative. The parameters k and r are fixed in advance and not estimated.

The special case in which exposure is at a constant rate d in the interval $[s_1, s_2]$ and is zero elsewhere is of particular interest. It can be shown, either by using (A12) and (A13) or by integrating (A11) directly, that

$$H_2(t) = \frac{db_1(\pi a_i)}{k!a_1}\begin{cases} 0 & t < s_1 \\ (t - s_1)^k & s_1 \leq t < s_2 \\ (t - s_1)^k - (t - s_2)^k & s_2 \leq t \end{cases} \qquad \text{(A19)}$$

if the first stage is affected (r = 1),

$$H_2(t) = \frac{db_{k-1}(\pi a_i)}{k!a_{k-1}}\begin{cases} 0 & t < s_1 \\ t^k - s_1^{k-1}[kt - (k - 1)s_1] & s_1 \leq t < s_2 \\ s_2^{k-1}[kt - (k-1)s_2] - s_1^{k-1}[kt - (k-1)s_1] & s_2 \leq t. \end{cases} \qquad \text{(A20)}$$

if the penultimate stage is affected (r = k - 1), and

$$H_2(t) = \frac{db_k(\pi a_i)}{k!a_k}\begin{cases} 0 & t < s_1 \\ t^k - s_1^k & s_1 \leq t < s_2 \\ s_2^k - s_1^k & s_2 \leq t \end{cases} \qquad \text{(A21)}$$

if the last stage is affected (r = k).

If exposure is instantaneous (or nearly so) at time s_1 to a total dose D, the subsequent risk can be derived by taking limiting cases of the above results. The expressions obtained are:

$$H_2(t) = \frac{Db_1(\pi a_i)}{(k-1)!a_1}(t - s_1)^{k-1} \qquad t > s_1 \qquad \text{(A2}$$

for the case for which only the first transition is affected (r = 1);

$$H_2(t) = \frac{Db_{k-1}(\prod a_i)}{(k-2)!a_{k-1}} s_1^{k-2}(t - s_1) \qquad t > s_1 \tag{A23}$$

for the case for which only the penultimate transition is affected ($r = k-1$); and

$$H_2(t) = \frac{Db_k(\prod a_i)}{(k-1)!a_k} s_1^{k-1} \qquad t > s_1 \tag{A24}$$

for the case for which only the last transition is affected ($r = k$).

A1.2 Case in which two stages are dose-related: Suppose stages r and ($r < \ell$) are dose-related; that is, $b_r > 0$, $b_\ell > 0$, and $b_i = 0$ otherwise. The hazard function (A7) can now be written

$$H(t) = (\prod a_i) \int_0^t \int_0^{u_k} \ldots \int_0^{u_2} [1 + (b_r/a_r)D(u_r) + (b_\ell/a_\ell)D(u_\ell) \tag{A25}$$

$$+ b_r b_\ell D(u_r)D(u_\ell)/(a_r a_\ell)]du_1 \ldots du_k.$$

This integral can be broken up into 4 pieces, 3 of which we have already evaluated. Assuming that $D(t)$ is the step-function (A13), it follows that

$$H(t) = q_0 t^k + q_r Z_{rk}(t) + q_\ell Z_{\ell k}(t) + q_{r\ell} Z_{r\ell k}(t) \tag{A26}$$

where q_0, q_r, $Z_{rk}(t)$, q_ℓ, and $Z_{\ell k}(t)$ have all been defined previously, and $q_{r\ell}$ is defined as

$$q_r = (\prod a_i)[b_r b_\ell/(a_r a_\ell)]/k! \tag{A27}$$

All that remains is to evaluate

$$Z_{r\ell k}(t) = k!\int_0^t \int_0^{u_k} \cdots \int_0^{u_2} D(u_\ell) D(u_r)\, du_1 \ldots du_k \tag{A28}$$

$$= k!\int_0^t \int_0^{u_k} \cdots \int_0^{u_{\ell+1}} D(u_\ell) Z_{r\ell-1}(u_\ell)\, du_\ell \ldots du_k .$$

Using the expressions developed previously for Z_{rk} and reversing the order of integration, we reduce this expression to the single integral

$$Z_{r\ell k}(t) = \int_0^t \sum_{j=0}^{\ell-1-r} \frac{(-1)^j \quad k!}{j!(r-1)!(\ell-1-r-j)!(j+r)} \left[G(j+r,x-1) u_\ell^{\ell-1-r-j} + h_x u_\ell^{\ell-1}\right] \frac{D(u_\ell)(t-u_\ell)^{k-\ell}}{(k-\ell)!}\, du_\ell \tag{A29}$$

where x is the function of u_ℓ defined by $s_{x-1} \leq u_\ell < s_x$. The term G(j+r, x-1) is thus a step-function in u_ℓ that has jumps at the same points as $D(u_\ell)$. The integral (A29) is evaluated by expanding $(t - u_\ell)^{k-\ell}$ in a binomial series. The result is

$$Z_{r\ell k}(t) = \sum_{i=0}^{k-\ell} \sum_{j=0}^{\ell-1-r} \frac{(-1)^{i+j} k!\, t^{k-\ell-i}}{i!j!(\ell-1-r-j)!(k-\ell-i)!(r+j)} \cdot$$

$$\left[\sum_{n=1}^{m-1} \left\{\frac{[h_n G(r+j,n-1) - h_{n+1} G(r+j,n)] s_n^{\ell+i-r-j}}{\ell+i-r-j} + \frac{(h_n^2 - h_{n+1}^2) s_n^{i+\ell}}{\ell+i}\right\} + \frac{h_m G(r+j,\, m-1) t^{\ell+i-r-j}}{\ell+i-r-j} + \frac{h_m^2 t^{\ell+i}}{\ell+i}\right] \tag{A30}$$

where m satisfies $s_{m-1} \leq t < S_m$. The implementation of this equation by the computer is not as difficult as it looks, as a number of the sums can be calculated a single time and recalled when needed.

The delay δ is included here also and consequently the computer program estimates the 5 parameters q_0, q_r, q_ℓ, $q_{r\ell}$, and δ, each of which is constrained (only) to be non-negative. Note that this is a more generalized form than that predicted by the Armitage-Doll theory because it does not include the constraint $q_{r\ell}q_0 = q_r q_\ell$ which is implied by equations (A17), (A18), and (A27).

A2. Description of Computer Programs

The parameters q_0, q_r,..., and δ are estimated by maximizing the likelihood of the data. Denote the dependence of the probability P(t) upon the dose pattern d(t) by writing P(t) = P(t;D). Parameters of interest in risk assessment include the extra risk by a given age t from a given dose pattern D defined as

$$R(t;D) = \frac{P(t;D) - P(t;0)}{1 - P(t;0)} \tag{A31}$$

and the dose scale parameter f defined as the solution to

$$\frac{P(t;fD) - P(t;0)}{1 - P(t;0)} = \pi \tag{A32}$$

where π is a specified amount of extra risk and D is a specified dose pattern. Thus, f is the amount by which a given dose pattern D must be multiplied to produce an extra risk of π.

Confidence limits for extra risk and f are computed using the asymptotic distribution of the likelihood ratio statistics.(26-27)

For example, the 95% lower confidence limit for f is defined as the minimum f which satisfies (A29) and

$$2(L_{max} - L) = (1.645)^2$$

where L is the log-likelihood of the data and L_{max} is the maximum value of the log-likelihood.